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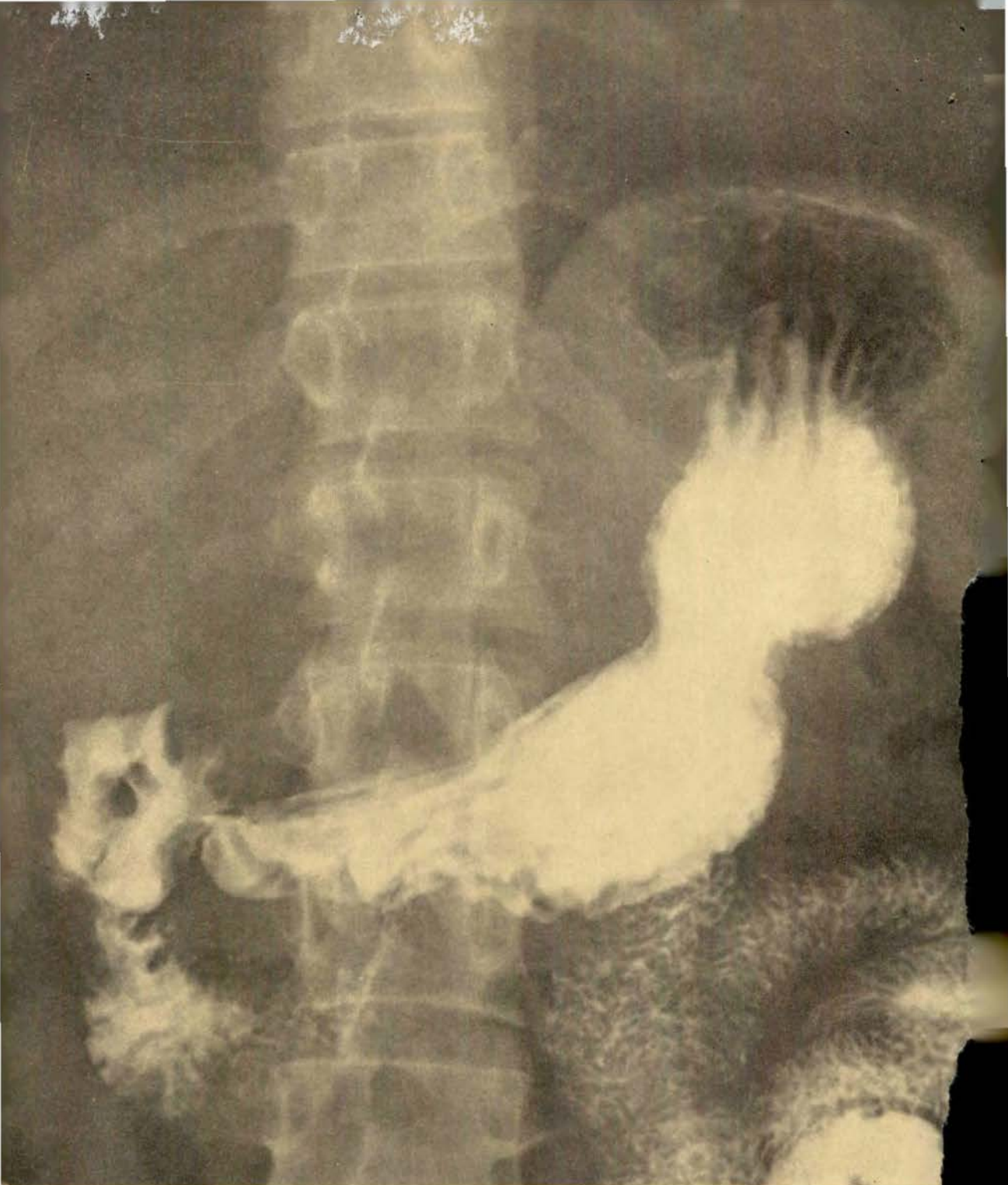
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CONTENTS OF VOLUME 87

JANUARY, 1962, NUMBER 1

A Theme for a Radiation Therapy Center. The President's Address. <i>Jesshill Love, M.D.</i>	3
Policies of Treatment in Cancer of the Cervix Uteri. <i>Gilbert H. Fletcher, M.D., Felix N. Rutledge, M.D., and Paul M. Chau, M.D.</i>	6
Complications in High Dose Whole Pelvis Irradiation in Female Pelvic Cancer. <i>Paul M. Chau, M.D., Gilbert H. Fletcher, M.D., Felix N. Rutledge, M.D., and Gerald D. Dodd, Jr., M.D.</i>	22
Pyelographic Analysis of Radiation Therapy in Carcinoma of the Cervix. <i>Robert K. Rhamy, M.D., and Richard W. Stander, M.D.</i>	41
The Use of a Diamond Shaped Field in Irradiation of Pelvic Organs, Particularly in Carcinoma of the Cervix Uteri. <i>Charles Botstein, M.D., R. J. Schulz, M.S., and Norman Simon, M.D.</i>	44
Can Radiosensitivity and Histopathology of Cervical Cancer Be Correlated? <i>Arthur T. Hertig, M.D., and Hazel Gore, M.B., B.S.</i>	48
Cytologic Prognosis in Cancer of the Cervix; Two Year Survival Rates in a Randomized Series. <i>Ruth M. Graham, Sc.D. (Hon.), and John B. Graham, M.D.</i>	56
Radiosensitivity Testing of Cervix Cancer By the Test Dose Technique. <i>S. B. Gusberg, M.D., and Grace G. Herman, M.D.</i>	60
Oleic Acid I ¹³¹ Intestinal Absorption in Pelvic Cobalt 60 Irradiation. <i>Jack K. Goodrich, M.D., and Bernard T. Hickman, M.D.</i>	69
Mammography of Breast Sarcoma. <i>S. M. Berger, M.D., and J. Gershon-Cohen, M.D., D.Sc. (Med.)</i>	76
Breast Cancer; Five Year Results: Two Random Series of Simple Mastectomy with Postoperative Irradiation Versus Extended Radical Mastectomy. <i>Sigvard Kaae, and Helge Johansen.</i>	82
The Measurement of Build-Up on Curved Surfaces Exposed to Co ⁶⁰ and Cs ¹³⁷ Beams. <i>R. S. Bush, and H. E. Johns.</i>	89
Actinomycin D and Radiation Therapy. <i>Edwin J. Liebner, M.D.</i>	94
Clinical and Biologic Studies of Actinomycin D and Roentgen Irradiation. <i>Giulio J. D'Angio, M.D.</i>	106
Primary Carcinoma of the Pituitary. <i>Thomas H. Newton, M.D., H. Joachim Burhenne, M.D., and Alphonse J. Palubinskas, M.D.</i>	110
Reticulum Cell Sarcoma of Bone. <i>Patrick A. Dolan, M.D.</i>	121
Medical Scintillation Scanning Utilizing Closed Circuit TV Contrast Enhancement; Technical Aspects. <i>Lieutenant Commander William H. Fleming, MC USNR, Lieutenant Commander James D. McIlraith, MSC USN, and Captain E. Richard King, MC USN.</i>	128
Detection of Liver Tumors with Colloidal Radiogold; A New Method of High-Contrast Photoscanning. <i>K. H. Ephraim, M.D.</i>	141
The Use of I ¹²⁵ to Increase Isotope Scanning Resolution. <i>Harold Endlich, M.D., Paul Harper, M.D., Robert Beck, B.S., Warren Siemens, and Katherine Lathrop, M.S.</i>	148
Some Modifications of Photoscanning Techniques. <i>Harold L. Endlich, M.D.</i>	156
Delineation of Human Kidneys by Scintillation Scanning. <i>Robert D. Westphal, M.D., J. R. Risser, Ph.D., Donald Motzkin, M.D., Ethel E. Erickson, M.D., and Mary C. Morgan, M.D.</i>	161
The Relation of Radioiodine Dosimetry to Results and Complications in the Treatment of Metastatic Thyroid Cancer. <i>Richard S. Benua, M.D., Norma R. Cicale, Martin Sonenberg, M.D., Ph.D., and Rulon W. Rawson, M.D.</i>	171
Laboratory Production of Short Lived Radioisotopes. <i>A. E. Caswell, B.S.</i>	183
An Instrumented Phantom System for Analog Computation of Treatment Plans. <i>Samuel W. Alderson, B.A., Lawrence H. Lanzl, Ph.D., Marvin Rollins, M.D., and Jack Spira, Ph.D.</i>	185
Officers.....	196
Editorials	
The Forty-fourth Annual Meeting of the American Radium Society. <i>Robert L. Brown, M.D.</i> ...	197
John William Pierson, 1883-1961. <i>Webster H. Brown, M.D.</i>	199
Preliminary Program of The American Radium Society.....	201
National Committee on Radiation Protection and Measurements.....	204
News Items.....	206
Book Reviews.....	209
Books Received.....	210
Society Proceedings.....	211
Abstracts of Radiological Literature.....	216

FEBRUARY, 1962, NUMBER 2

The Azygos Vein Arch and Its Valvular Apparatus; Angiographic Observations. <i>Giulio Tori, M.D., and G. F. Garusi, M.D.</i>	235
Dilatation of the Hemiazygos Veins in Superior Vena Caval Occlusion Simulating Mediastinal Tumor. <i>Israel Steinberg, M.D.</i>	248
Experimental Coronary Arteriography Using Roentgenographic Magnification. <i>Timothy Takaro, M.D., Stewart M. Scott, M.D., and William H. Sewell, M.D.</i>	258
Percutaneous Arterial Catheterization and Its Application. <i>Kurt Amplatz, M.D.</i>	265
The Use of Percutaneous Transfemoral Aortography to Diagnose Abnormalities of the Renal Arteries. <i>James M. Stokes, M.D., and Erik Carlsson, M.D.</i>	276
Hepatic Artery Aneurysm; Case Report. <i>James L. Quinn, III, M.D., and James F. Martin, M.D.</i> ...	284
Uterine Arteriography in Hydatidiform Mole. <i>Jaime Roca, Ruben Villamayor, José Llauro, and Rafael Flichtentrei</i>	287
An Approach to Femoral Arteriography; A Long Film Changer. <i>Fred C. Shipp, M.D.</i>	291
The Jet Sign in the Angiocardiographic Diagnosis of Anomalous Pulmonary Venous Drainage. <i>Israel Steinberg, M.D., and Daniel S. Lukas, M.D.</i>	294
Angiographic Patterns of Cerebral Convexity Veins and Superficial Dural Sinuses. <i>Giovanni Di Chiro, M.D.</i>	308
The Posterior Inferior Cerebellar Artery on Vertebral Angiography. <i>Bernard S. Wolf, M.D., Charles M. Newman, M.D., and Mansho T. Khilnani, M.D.</i>	322
The Significance of Protein Binding of Contrast Media in Roentgen Diagnosis. <i>Elliott C. Lasser, M.D., Richard S. Farr, M.D., Tak Fujimigari, M.D., and Walter N. Tripp, M.D.</i>	338
A Modified Lumbar Puncture Needle for Pneumoencephalography. <i>Bernard S. Epstein, M.D., and Joseph A. Epstein, M.D.</i>	361
Three Simple Devices to Facilitate Contrast Neuroroentgenography. <i>M. M. Schechter, M.D., and Lawrence Strenger, M.D.</i>	363
An Autotomographic Appliance. <i>Edmund H. Burrows, M.B., Ch.B., D.M.R.D.</i>	366
Primary Spinal Tumors: A Seven-Year Study. <i>Arthur S. Tucker, M.D., Bisamai Aramsri, M.D., and W. James Gardner, M.D.</i>	371
Bronchogenic Carcinoma; A Comparative Study of the Palliative Effects of Radiation Therapy, Radiation Therapy Plus Nitrogen Mustard, and Radiation Therapy Plus Amethopterin and Actinomycin D in Combination. <i>Leslie L. Alexander, M.D., Julia Causing, M.D., Harold N. Schwinger, M.D., and Min Chiu Li, M.D.</i>	375
Sialography of the Submaxillary Salivary Gland; A New Technique. <i>S. Gordon Castigliano, M.D., F.A.C.S.</i>	385
Detail Visibility in Radiographs: An Experimental and Theoretical Study of Geometric and Absorption Unsharpness. <i>K. Rossmann, Ph.D.</i>	387
Duplication of Roentgenograms by Solarization. <i>Joshua A. Becker, M.D., and Dewey P. Blackstone, R.T.</i>	394
Officers.....	397
Editorial	
Radiation Registry of Physicians.....	398
News Items.....	400
Book Reviews.....	403
Books Received.....	404
Abstracts of Radiological Literature.....	405

MARCH, 1962, NUMBER 3

Oral Cancer: A Twenty-Five Year Study. Janeway Lecture, 1961. <i>Clifford L. Ash, M.D.</i>	417
Necrosis in Treatment of Intraoral Cancer by Radiation Therapy. <i>William S. MacComb, M.D.</i>	431
Distant Metastases from Head and Neck Cancer. <i>Sidney Rubensfeld, M.D., Gustave Kaplan, M.D., and Adrian A. Holder, M.D.</i>	441
Localization of Brain Tumors Using Radioiodinated Human Serum Albumin. <i>Edward B. Schlesinger, M.D., Sheila deBoves, B.A., and Juan Taveras, M.D.</i>	449
Radiation Therapy in the Treatment of Intracranial Tumors. <i>Robert J. Bloor, M.D., Arch W. Templeton, M.D., and Raymond S. Quick, B.Sc.</i>	463
Should We Treat Glioblastoma Multiforme? A Study of Survival in 425 Cases. <i>Juan M. Taveras, M.D., Hartwell G. Thompson, Jr., M.D., and J. Lawrence Pool, M.D.</i>	473

The Radium Treatment of Recurrent Cancer of the Uterine Cervix. <i>J. Ernest Breed, B.S., M.D.</i> . . .	480
Comparative Study of Supervoltage Radiotherapy Techniques in Some Pelvic Malignancies. <i>José Noriega L., M.D., D.M.R. (London), and Armando López, M.D.</i> . . .	488
Isodose Curves and Radiation Distribution about Patients with Intracavitary Radium Sources. <i>Hans-Guenter Wandel, M.D.</i> . . .	500
Radiotherapy of Ewing's Sarcoma. <i>Paul W. Scanlon, M.D.</i> . . .	504
Clinical Use of Short Source-Skin Distance Cesium 137 Teletherapy Unit. <i>Gilbert H. Fletcher, M.D., Gordon C. Johnson, M.D., Warren K. Sinclair, Ph.D., and Arthur Cole, Ph.D.</i> . . .	511
A Cesium Head and Neck Unit. <i>M. Lederman, M.B., D.M.R.E., F.F.R.</i> . . .	521
Common Medical Problems in Radiotherapy Patients. <i>Arvin S. Glicksman, M.D.</i> . . .	525
Hemipelvectomy in the Treatment of Advanced Cancer. <i>Theodore R. Miller, M.D.</i> . . .	531
Effects of the Combined Action of Roentgen Rays and a Chemical Carcinogen (DAB) on the Rat's Liver. <i>Antoine Lacassagne, and Lucienne Hurst</i> . . .	536
The Systemic Effects of Localized Radiation on Serum Proteins in Humans; A Preliminary Report. <i>Joseph L. Ackerman, M.D., Joseph A. Linsk, M.D., and Bernard J. Schuman, M.D.</i> . . .	543
Postirradiation Treatment of Lethal Total Body Irradiation by Cell-Free Spleen Extracts. <i>Friedrich Ellinger, M.D.</i> . . .	547
Preliminary Reports of Chromosome Studies during Radiation Therapy. <i>Robert C. Goodlin, M.D.</i> . . .	555
Low Levels of X-Irradiation and the Early Mammalian Embryo. <i>Roberts Rugh</i> . . .	559
The Influence of the Time Factor on the Dose-Response Curve. <i>Lucille A. Du Sault</i> . . .	567
The Second Half-Value Layer and the Homogeneity Coefficient. <i>E. Dale Trout, B.S., D.Sc., John P. Kelley, B.S., and Arthur C. Lucas, B.S.</i> . . .	574
Dosimetry by Tomography in Interstitial Curietherapy: Point Technique. <i>B. Pierquin, M.D., and J. V. Fayos, M.D.</i> . . .	585
World Survey of Radioisotope Teletherapy Units. <i>K. C. Tsien</i> . . .	593
Officers . . .	600
Editorials . . .	
A Concept of Radiosensitivity. <i>J. Robert Andrews</i> . . .	601
The Undergraduate Teaching of Radiation Therapy. <i>Philip Rubin, M.D.</i> . . .	606
Gioacchino Failla, 1891-1961. <i>Harald H. Rossi, Ph.D.</i> . . .	608
News Items . . .	611
National Bureau of Standards; Scattering from a Cobalt 60 Calibrating Source . . .	612
Book Reviews . . .	614
Books Received . . .	616
Society Proceedings . . .	617
Abstracts of Radiological Literature . . .	622

APRIL, 1962, NUMBER 4

The Use of Silicone Foam for Examining the Human Sigmoid Colon. <i>Galen B. Cook, M.D., and Alexander R. Margulis, M.D.</i> . . .	633
Performing the Barium Enema: Equipment, Preparation, and Contrast Medium. <i>Howard L. Steinbach, M.D., and H. Joachim Burhenne, M.D.</i> . . .	644
The Diagnosis and Treatment of Dilatation of the Colon in Severe Ulcerative Colitis; A Diagnostic Roentgen Sign. <i>Manfred Simon, M.D., Jerome H. Shapiro, M.D., Julius G. Parker, M.D., Clarence J. Schein, M.D., and Berthold Weingarten, M.D.</i> . . .	655
Diffuse Lymphomatous Disease of the Colon: Its Roentgen Appearance. <i>Rubem Pochaczewsky, M.D., and Robert S. Sherman, M.D.</i> . . .	670
Preparation of the Colon for Barium Enema Study; A Comparative Evaluation of Three Techniques. <i>Robert D. Sloan, M.D., and Jack K. Goodrich, M.D.</i> . . .	685
Preparation of the Colon for Barium Enema Examination; A Comparison of Three Agents. <i>John L. Ritan, CAPTAIN, USAF (MC)</i> . . .	690
Difficulties in the Roentgen Diagnosis of Cecal Tumors. <i>Norman Heilbrun, M.D., and Charles Bernstein, M.D.</i> . . .	693
Retrograde Prolapse of the Ileocecal Valve. <i>Sidney Rubin, M.D., David S. Dann, M.D., Charles Ezekial, M.D., and Jack Vincent, M.D.</i> . . .	706
A Histopathologic Basis for the Interpretation of Small Bowel Roentgenography in Tropical Sprue. <i>Martin H. Floch, M.D., William L. Caldwell, M.D., and Thomas W. Sheehy, M.D.</i> . . .	709
Further Roentgen Observations of the Small Intestine in Whipple's Disease. <i>Gene J. Triano, M.D.</i> . . .	717
Coiling of the Long Tube in the Small Intestine; A Sign of Intestinal Obstruction. <i>Leo S. Figiel, M.D., and Steven J. Figiel, M.D.</i> . . .	721

An Evaluation of Radiopaque Substances for Intestinal Decompression Tubes. <i>Meyer O. Cantor, M.D.</i>	724
Calcified Gastric Leiomyoma. <i>Andrew B. Crummy, Jr., M.D., and John H. Juhl, M.D.</i>	727
Prolapse of Gastric Mucosa; Report of an Unusual Case. <i>Ching Tseng Teng, M.D.</i>	729
Acute Hemorrhagic Pancreatitis Complicated by Duodenal Obstruction; Report of a Case. <i>Raymond Brust, Jr., M.D., and Kuei-Chi Chen, M.D.</i>	732
Chronic Cholecystitis; Indications for Revision of the Clinical Diagnosis. <i>Edwin L. Lame, M.D.</i>	736
Pneumatic Compression Paddle (Prone Pressure Device) in Cholecystography and Choledochography. <i>Joseph F. Linsman, M.D.</i>	740
A Double Blind Study of Oragrafin and Telepaque. <i>W. Wallace White, M.D., and Harry W. Fischer, M.D.</i>	745
Adherent Gallbladder Simulating an Intrinsic Lesion of the Right Side of the Colon; Report of a Case. <i>S. David Rockoff, M.D., and William J. Tuddenham, M.D.</i>	749
The Reappearing Gallbladder. <i>Harold P. Lipton, M.D., and A. Bradley Soule, M.D.</i>	752
Milk of Calcium Renal Stone. <i>Robert A. W. Pullman, M.D., and Robert J. King, M.D.</i>	760
The Significance of the Lateral View in T-Tube Cholangiography. <i>William Z. Stern, M.D., Clarence J. Schein, M.D., and Harold G. Jacobson, M.D.</i>	764
Roentgenologic Study of the Topography of the Choledcho-Duodenal Junction. <i>Armin Schwartz, M.D., and David Birnbaum, M.D.</i>	772
Roentgenologic Manifestations of Primary Hepatoma with Particular Reference to Some Unusual Cholecystographic Findings. <i>Raymond W. Brust, Jr., M.D., and Peter C. Conlon, F.F.R.</i>	777
Officers	787
Editorials	
Polypoid Lesions of the Gallbladder. <i>Seymour Fiske Ochsner, M.D.</i>	788
Fred M. Hodges, 1887-1961. <i>Hunter B. Frischkorn, M.D.</i>	790
News Items	792
Books Received	795
Abstracts of Radiological Literature	797

MAY, 1962, NUMBER 5

Palate and Pharynx: Roentgenographic Evaluation in the Management of Cleft Palate and Related Deformities. <i>William C. Owsley, Jr., M.D.</i>	811
Contrast Laryngography in the Evaluation of Laryngeal Neoplasms. <i>Jacob I. Fabrikant, M.D., George J. Richards, Jr., M.D., Gabriel F. Tucker, Jr., M.D., and Robert J. Dickson, M.D.</i>	822
Anesthesia for Bronchography Utilizing Intermittent Positive Pressure Breathing Apparatus. <i>William Molnar, M.D., and John A. Prior, M.D.</i>	836
Transtacheal Bronchography; Complications of Injection outside the Trachea. <i>S. D. Zucherman, M.D., and George Jacobson, M.D.</i>	840
Tracheal Collapse in Polychondritis. <i>John W. Horns, M.D., and Bernard J. O'Loughlin, M.D., Ph.D.</i>	844
Granulomatous Lung Reaction following Repeat Bronchography with Propylidone. <i>Gilbert H. Friedell, M.D., Seymour A. Kaufman, M.D., Eugene G. Laforet, M.D., and John W. Strieder, M.D.</i>	847
Broncholar Behavior in Pulmonary Emphysema and in Bronchiectasis. <i>Joseph K. Isley, Jr., James Bacos, John B. Hickam, and George J. Baylin</i>	853
Primary Pulmonary Cryptococcosis; Case Report. <i>Robert D. Bahr, M.D., Harold Satz, M.D., and Vaso L. Purlia, M.D.</i>	859
Regional Roentgen Manifestations of Histoplasmosis. <i>Enrique Schwarz, M.D.</i>	865
Roentgen Findings in Terminal Bronchiolar Carcinoma. <i>Richard D. Kittredge, M.D., and Robert S. Sherman, M.D.</i>	875
Angiography As a Means of Determining Resectability of Primary Lung Cancer. <i>D. E. Sanders, M.D., F.R.C.P.(C), N. C. Delarue, B.A., M.D.M.S. (Tor), F.R.C.S.(C), F.A.C.S., F.C.C.P., and G. Lau, B.Sc., M.D.</i>	884
The Roentgenologic Signs of Pedunculated Pleural Tumors. <i>Alfred S. Berne, M.D., and E. Robert Heitzman, M.D.</i>	892
Post-Traumatic Herniation of the Lung. <i>Donald A. Taylor, M.D., and Harold G. Jacobson, M.D.</i>	896
The Axillary Mass Sign on Lateral Chest Roentgenograms. <i>Frederick J. Bonte, M.D., and Murry D. Schonfeld, M.D.</i>	900
Calcified Pulmonary Artery Thrombus. <i>William H. McAlister, M.D., and Ethyl Blatt, M.D.</i>	908
The Cinefluorographic Approach to the Diagnosis of Pericardial Effusion. <i>Joseph Jorgens, M.D., Ph.D., Robert Kundel, M.D., and Arthur Lieber, M.D.</i>	911
Agenesis of a Main Branch of the Pulmonary Artery. <i>D. W. Sherrick, M.D., Owings W. Kincaid, M.D., and James W. DuShane, M.D.</i>	917
The Normal Roentgenographic Measurement of the Right Descending Pulmonary Artery in 1,085 Cases. <i>C. H. (Joseph) Chang, M.D.</i>	929

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No. 1

CONTENTS

<i>A Theme for a Radiation Therapy Center. The President's Address.</i> JESSHILL LOVE, M.D.	3
<i>Policies of Treatment in Cancer of the Cervix Uteri.</i> GILBERT H. FLETCHER, M.D., FELIX N. RUTLEDGE, M.D., AND PAUL M. CHAU, M.D.	6
<i>Complications in High Dose Whole Pelvis Irradiation in Female Pelvic Cancer.</i> PAUL M. CHAU, M.D., GILBERT H. FLETCHER, M.D., FELIX N. RUTLEDGE, M.D., AND GERALD D. DODD, JR., M.D.	22
<i>Pyelographic Analysis of Radiation Therapy in Carcinoma of the Cervix.</i> ROBERT K. RHAMY, M.D., AND RICHARD W. STANDER, M.D.	41
<i>The Use of a Diamond Shaped Field in Irradiation of Pelvic Organs, Particularly in Carcinoma of the Cervix Uteri.</i> CHARLES BOTSTEIN, M.D., R. J. SCHULZ, M.S., AND NORMAN SIMON, M.D.	44
<i>Can Radiosensitivity and Histopathology of Cervical Cancer Be Correlated?</i> ARTHUR T. HERTIG, M.D., AND HAZEL GORE, M.B., B.S.	48
<i>Cytologic Prognosis in Cancer of the Cervix; Two Year Survival Rates in a Randomized Series.</i> RUTH M. GRAHAM, Sc.D. (HON.), AND JOHN B. GRAHAM, M.D.	56
<i>Radiosensitivity Testing of Cervix Cancer By the Test Dose Technique.</i> S. B. GUSBERG, M.D., AND GRACE G. HERMAN, M.D.	60
<i>Oleic Acid I^{131} Intestinal Absorption in Pelvic Cobalt 60 Irradiation.</i> JACK K. GOODRICH, M.D., AND BERNARD T. HICKMAN, M.D.	69
<i>Mammography of Breast Sarcoma.</i> S. M. BERGER, M.D., AND J. GERSHON-COHEN, M.D., D.Sc. (MED.)	76
<i>Breast Cancer; Five Year Results: Two Random Series of Simple Mastectomy with Postoperative Irradiation Versus Extended Radical Mastectomy.</i> SIGVARD KAAE, AND HELGE JOHANSEN	82
<i>The Measurement of Build-Up on Curved Surfaces Exposed to Co^{60} and Cs^{137} Beams.</i> R. S. BUSH, AND H. E. JOHNS	89
<i>Actinomycin D and Radiation Therapy.</i> EDWIN J. LIEBNER, M.D.	94

(Continued on p. iv)

<i>Clinical and Biologic Studies of Actinomycin D and Roentgen Irradiation.</i>	
GIULIO J. D'ANGIO, M.D.	106
<i>Primary Carcinoma of the Pituitary.</i> THOMAS H. NEWTON, M.D., H.	
JOACHIM BURHENNE, M.D., AND ALPHONSE J. PALUBINSKAS, M.D.	110
<i>Reticulum Cell Sarcoma of Bone.</i> PATRICK A. DOLAN, M.D.	121
<i>Medical Scintillation Scanning Utilizing Closed Circuit TV Contrast Enhancement; Technical Aspects.</i> LIEUTENANT COMMANDER WILLIAM H. FLEMING, MC USNR, LIEUTENANT COMMANDER JAMES D. McILRAITH, MSC USN, AND CAPTAIN E. RICHARD KING, MC USN	128
<i>Detection of Liver Tumors with Colloidal Radiogold; A New Method of High-Contrast Photoscanning.</i> K. H. EPHRAIM, M.D.	141
<i>The Use of I^{125} to Increase Isotope Scanning Resolution.</i> HAROLD ENDLICH, M.D., PAUL HARPER, M.D., ROBERT BECK, B.S., WARREN SIEMENS, AND KATHERINE LATHROP, M.S.	148
<i>Some Modifications of Photoscanning Techniques.</i> HAROLD L. ENDLICH, M.D.	156
<i>Delineation of Human Kidneys by Scintillation Scanning.</i> ROBERT D. WESTPHAL, M.D., J. R. RISSE, PH.D., DONALD MOTZKIN, M.D., ETHEL E. ERICKSON, M.D., AND MARY C. MORGAN, M.D.	161
<i>The Relation of Radioiodine Dosimetry to Results and Complications in the Treatment of Metastatic Thyroid Cancer.</i> RICHARD S. BENUA, M.D., NORMA R. CICALA, MARTIN SONENBERG, M.D., PH.D., AND RULON W. RAWSON, M.D.	171
<i>Laboratory Production of Short Lived Radioisotopes.</i> A. F. CASWELL, B.S.	183
<i>An Instrumented Phantom System for Analog Computation of Treatment Plans.</i> SAMUEL W. ALDERSON, B.A., LAWRENCE H. LANZL, PH.D., MARVIN ROLLINS, M.D., AND JACK SPIRA, PH.D.	185
<i>Officers</i>	196
<i>Editorials</i>	
<i>The Forty-fourth Annual Meeting of the American Radium Society.</i>	
ROBERT L. BROWN, M.D.	197
<i>John William Pierson, 1883-1961.</i> WEBSTER H. BROWN, M.D.	199
<i>Preliminary Program of The American Radium Society</i>	201
<i>National Committee on Radiation Protection and Measurements</i>	204
<i>News Items</i>	206
<i>Book Reviews</i>	209
<i>Books Received</i>	210
<i>Society Proceedings</i>	211
<i>Abstracts of Radiological Literature</i>	216

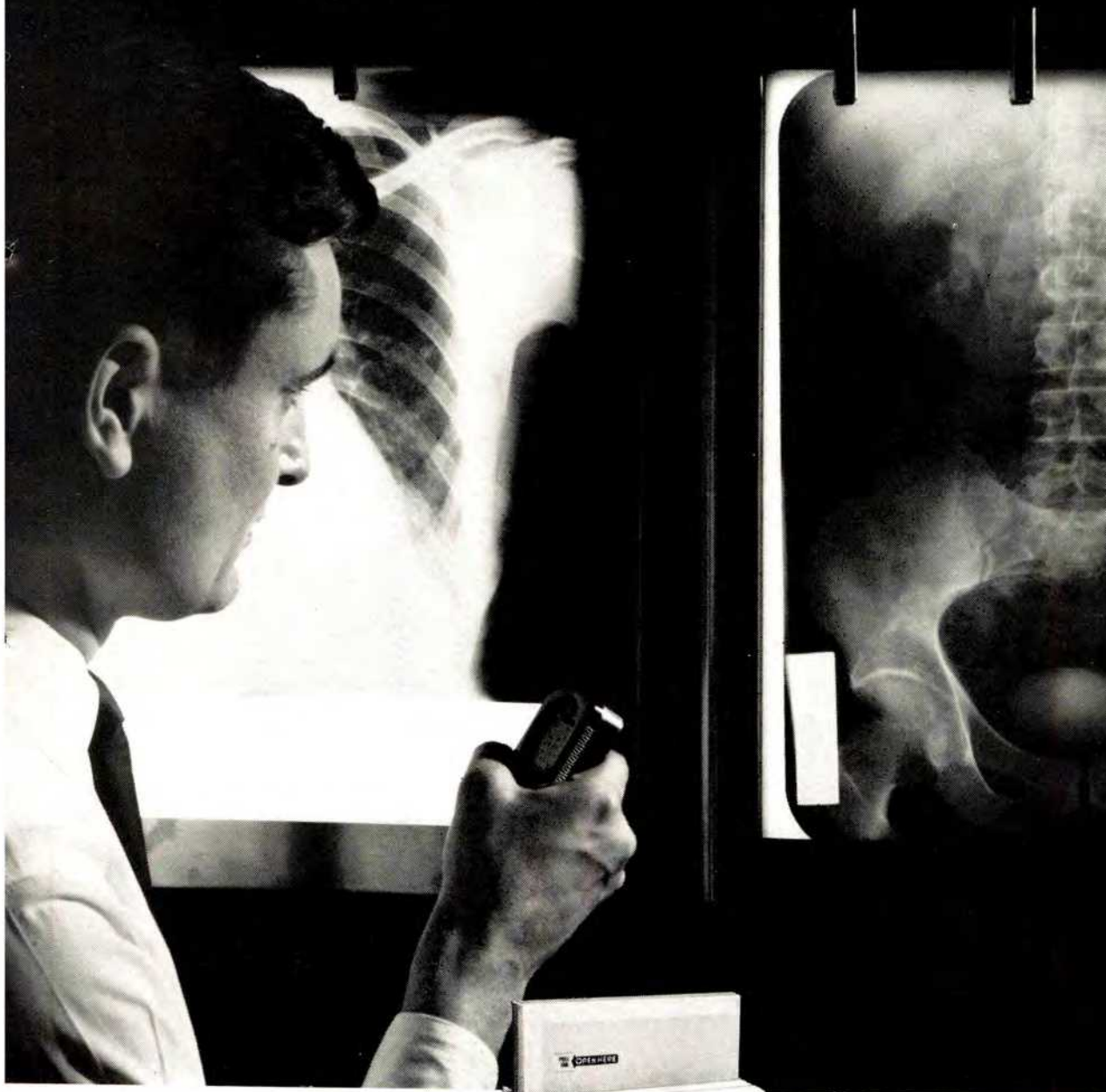
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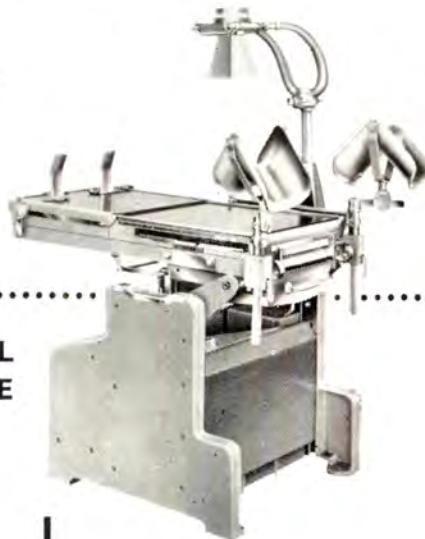


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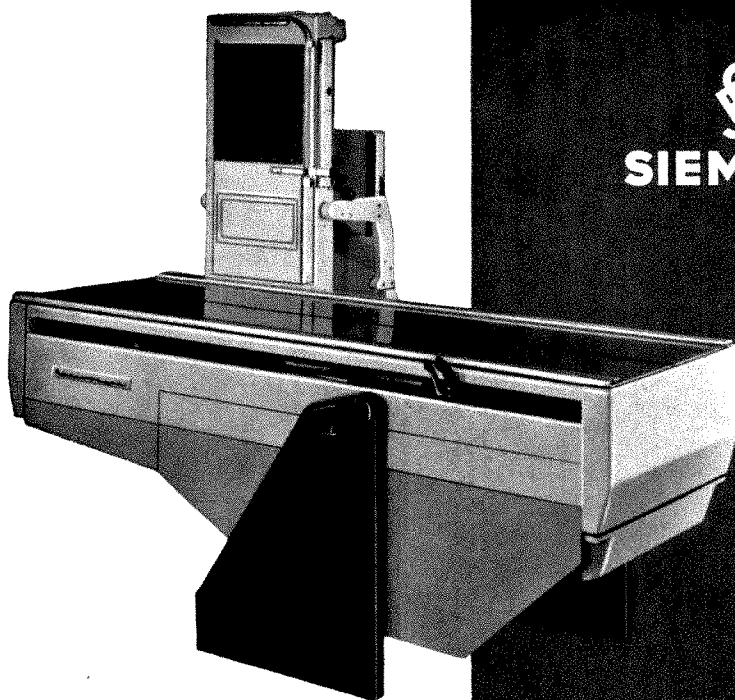
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JESSHILL LOVE, M.D.

THE AMERICAN JOURNAL OF ROENTGENOLOGY RADIUM THERAPY AND NUCLEAR MEDICINE

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No. 1

A THEME FOR A RADIATION THERAPY CENTER* THE PRESIDENT'S ADDRESS

By JESSHILL LOVE, M.D.
SANTA BARBARA, CALIFORNIA

OCCASIONALLY, during your office routine, you may have encountered a small experience that for some reason has haunted your memory, and may even in time have come to inspire long and searching thought. This happened to me a few weeks ago, when I was perusing an editor's copy of the 1961 Preliminary Program of the American Radium Society. Drs. Leucutia and Krabbenhoft had written at the top of each page of the Program the word *ONWARD*. As I turned the pages, I noticed the word again and again. It had a disturbing effect on me. Days later I found myself recalling the word, particularly when I was putting the Program into final form. In the end, it prompted me to take a long and thoughtful look at the progress of radiotherapy, our gain, our specialty, and our future.

I will not pretend that my cogitations resulted in a solution to our problems in radiation therapy and in cancer therapy; but I did, at any rate, decide, at that time, that I would tell you a little about how *one* community solved, for itself, the problem of acquiring adequate facilities and a full time radiotherapist for its center. And it occurred to me that the story of that community's achievement might prove instruc-

tive and encouraging to other communities, similarly circumstanced.

At the outset, however, let me say that I advocate no divergence from our present concept of nonregimented medical practice. Such divergence would, in my view, invite loss of individuality within the profession. It could mean in time the elimination of great leadership within the specialties: I think of such names as Charles Martin, William Harris, Janeway, Failla, Quimby and others, under whom the profession thrived and developed in the face of vigorous competition. This freedom and right of practice ought not to be tranquilized, so to speak, by compulsory subsidized governmental programs.

But the presence of our honored guests from England and Scandinavia is my cue to speak briefly on centralized radiation therapy as it might exist in this country. Up to now, development of radiotherapy in the United States has, of necessity, been slow because it has been incarcerated in radiology. Radiologists, in their turn, have found it difficult to amortize their investment in radiographic equipment and adequate radium and x-ray therapy plants, and to divide their time between the two pursuits.

* Presented at the Forty-third Annual Meeting of the American Radium Society, Colorado Springs, Colorado, May 10-14, 1961.

There is no doubt that cancer is a disease of great national importance, requiring special treatment and cadres of experienced physicians, physicists and technicians who devote all their time to this one phase of therapy. It seems obvious that radiotherapy should be conceived and organized as a special discipline. Men and women who devote all their time to one discipline soon accumulate a vast store of clinical knowledge and reference material; and institutions in our cities staffed by these full time specialists are certainly able to offer effective, comprehensive treatment.

Perhaps in the future cancer may be controlled by a chemical, an immunizing agent, or a selective virus. But, in the meantime, during the research stage, surgical and radiation treatment should be improved by continuous, repeated analysis of end results. The best source of measuring end results is the survival time of large series treated with the same modalities. A few states have hospitals that are dedicated to the care of indigent cancer cases. Several cities have community-endowed centers for private and for part-pay patients; but there are not enough of these centers to cover the needs of the smaller communities. Here is where the Santa Barbara story, which I set out originally to tell you about, fits in.

What was accomplished in Santa Barbara may well be the answer for other small communities, with their need for specialized radiation therapy and centralization of adequate facilities. The key thing in setting up such a center is securing a full-time well trained radiotherapist; and after that comes modern equipment. In the Santa Barbara experiment, these two essentials were realized by a radiologist,¹ who gave his last years of practice to the pioneering of the program locally. He foresaw the advantages of a supervoltage center that would serve the entire community. The plan was discussed intermittently for a number of years with several citizens, and

in 1949 a Foundation² was formed which accepted a gift that made possible the purchase of a million-volt generator. He suffered a fatal airplane accident and was succeeded by another radiologist,³ who devoted his remaining years to the therapeutic problems of the community, and who guided the Foundation in its development of a program approved by the Medical Society. The problem of centralizing radiation therapy in this moderate-sized city seems virtually solved by now. I should like to tell you a little about how the Foundation is organized.

It is supported by donations from friends and Associate Members. These Associates have their own organization that sends out information and newsletters of national interest to its members, who currently number about one thousand. Contributions are voluntary and many are continuing from year to year. A few are marked for indigent cases. The contributions of the Associates provide for the purchase of new equipment and furnishings. The Foundation's Board of Trustees, composed of 12 citizens, including 2 physicians, reviews the necessity of any large purchase, manages the endowment fund, and endorses new policies suggested by the Director.

There is a special group of 34 citizens, 5 of whom are physicians, who are Members of the Foundation. It is their function to convene an annual meeting for the purpose of reviewing new additions and the progress of the Foundation during the year. This group also functions as liaison between the Foundation and the public. Certain of the Trustees and several members of the Foundation continue to be the major benefactors.

The Board of Trustees chooses the Director after his approval by representatives of the Medical Society. His contract is approved by a medical board. It is the function of the Director to receive and to treat

¹ Henry J. Ullmann, M.D.

² Memorial Cancer Foundation, 2315 Bath Street, Santa Barbara, California.

³ James T. Case, M.D.

patients and to conduct the business as a private practice. He uses the equipment and all the facilities located in a separate building, which is connected to a hospital by a short corridor. He decides and arranges all patient management and determines all fees without interference. All bills are released under his name, and he pays the Foundation a percentage of the collections for the use of the facilities. The Foundation uses the returned percentage to pay rent, salaries of the personnel, maintenance, office expense and janitorial service. Deficits and the purchase of new equipment are covered by the endowment reserve fund.

With respect to special equipment, a wide range of radiation energy is available from 70 kv. to 1,000 kv., cesium 137 and cobalt 60. The isotope laboratory is equipped to perform all the useful procedures. There is a spectrometer-scaler, a

scintiscanner, well-counting with or without the spectrometer, and a dual matched probe rate meter and dual recorder.

The need for a program of centralized radiation therapy is especially acute in smaller communities. The success of the Foundation at Santa Barbara may serve, with the necessary modifications, as an example for such communities. The plan has worked well in Santa Barbara owing to the support it has received both from physicians and from radiologists. Approximately 95 per cent of all radiation therapy and isotope procedures within a radius of twenty miles are performed at the Foundation. The need for such specialized programs is everywhere recognized. We must meet this challenge by providing adequate treatment at properly equipped centers.

2315 Bath Street
Santa Barbara, California



POLICIES OF TREATMENT IN CANCER OF THE CERVIX UTERI*

By GILBERT H. FLETCHER, M.D.,† FELIX N. RUTLEDGE, M.D.,‡
and PAUL M. CHAU, M.D.†
HOUSTON, TEXAS

SINCE the beginning of the century when the Wertheim operation was devised and the first radium treatments were given, considerable progress has been made in understanding the spread of cancers of the uterine cervix. Insight into the effectiveness of radiation therapy and surgical procedures has been obtained and surgical and radiotherapeutic techniques are now based on anatomic data and clinical biology.

The relationship of the zones of effectiveness of intracavitary radium therapy and external irradiation to the routes of spread of carcinomas of the cervix is well known. These main routes of spread (Fig. 1) are:

1. Along the vaginal mucosa considerably beyond palpable or visible disease.

2. Into the myometrium of the lower uterine segment and from there to the fundus. This type of extension is more likely to occur with carcinomas originating in the endocervix.

3. Into the network of lymphatics of the paracervical areas around the ureters, laterally to the internal os and the lower uterine segment. This spread is frequent even in the early stages.¹⁵ From there, the disease spreads into the parametria and to the pelvic wall lymphatics (Fig. 2, A, B and C).

The routes of spread and incidence of involvement of the pelvic wall lymph nodes in the adenocarcinomas and adenocanthomas of the cervix are not definitely known because of the relative rarity of these histologic patterns, but it can be assumed that the routes of spread are similar to those of the squamous cell carcinomas.

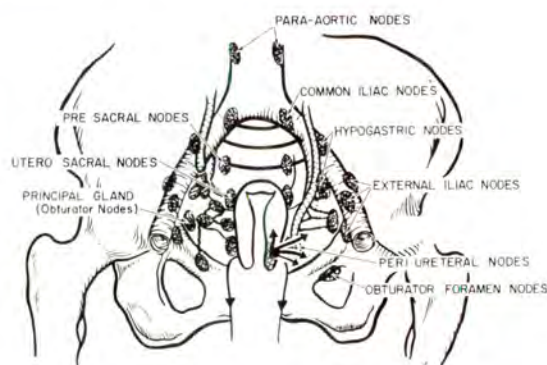


Fig. 1. Sketch of the routes of spread of cervical cancer. The arrows show the three main routes of spread along the vaginal mucosa, into the myometrium and into the lymphatics of the paracervical area. The lymph node areas are outlined in relationship to the bony structures, ureters and arteries. The lymph nodes located under the bifurcation of the common iliac artery (into the external iliac and the hypogastric arteries) are included with the hypogastric lymph nodes.

Originally, radiation treatment of patients with cancers of the uterine cervix consisted of only intracavitary radium. In the late 1920's, the addition of external irradiation, supplementing the intracavitary radium for irradiation of the parametria and pelvic walls, increased the survival rates in the Stage II and Stage III cases. Techniques of external irradiation and its combination with intracavitary radium therapy varied considerably between the various institutions.

In the 1930's, the 400 kv., 500 kv., and 800 kv. units became available. Several centers used 400 or 500 kv. units and half value layers (HVL) of 4 to 5 mm. Cu routinely.^{2,11,22,23} Higher doses were given

* Presented at the Sixty-first Annual Meeting of the American Roentgen Ray Society, Atlantic City, New Jersey, September 27-30, 1960.

† Department of Radiology, Section of Radiotherapy, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

‡ Department of Surgery, Chief of Gynecology Service.

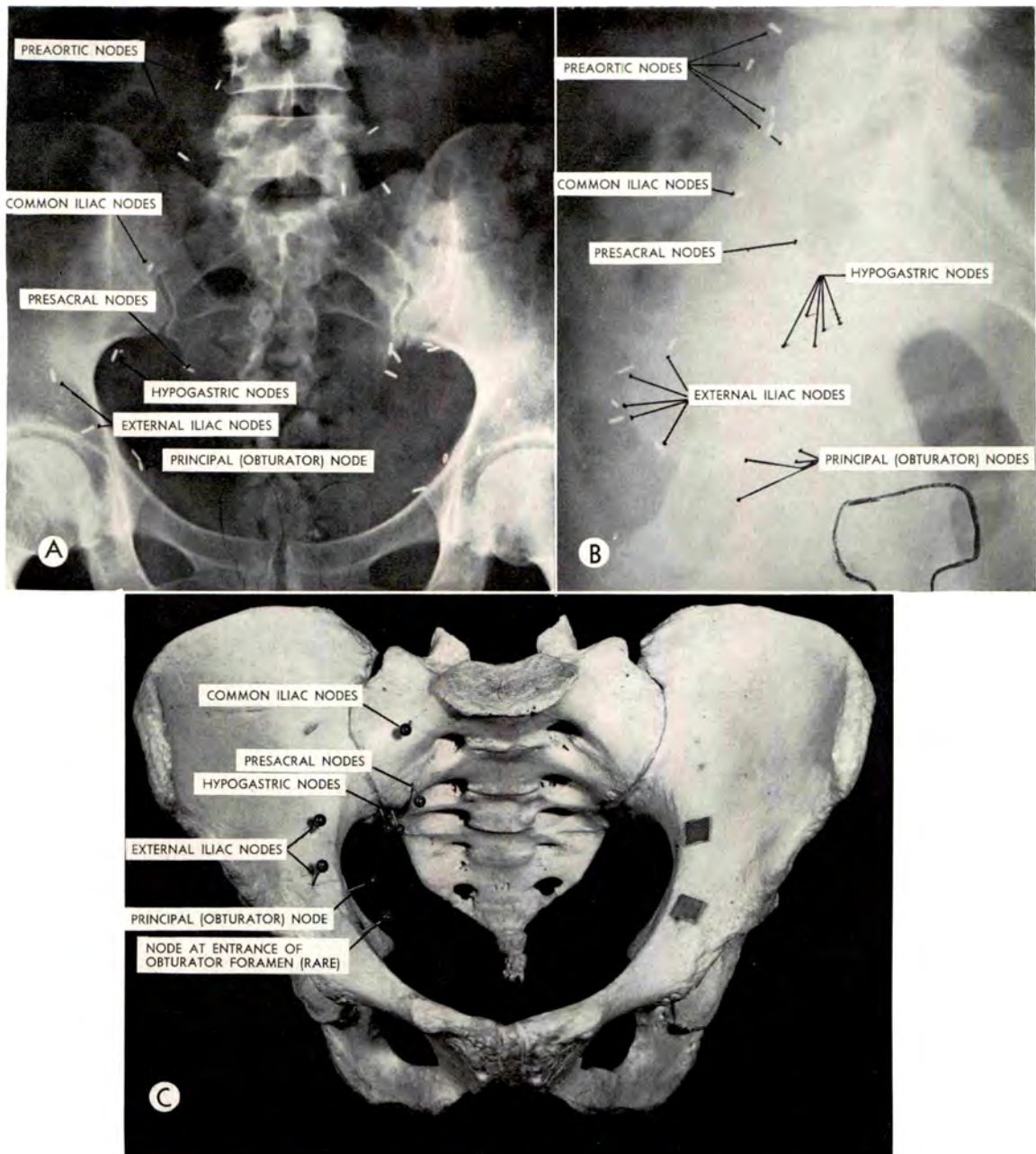


FIG. 2. Location of pelvic lymph nodes. (A) Anteroposterior roentgenogram of the pelvis, with lymph node locations identified by metallic clips attached during lymphadenectomy. The colpostats have been traced in the same relative position to the bony pelvis as they were on the roentgenograms taken with the applicators *in situ*. (B) Lateral roentgenogram of the pelvis of the same patient. Because of a small senile vagina, the vaginal applicators are low in relationship to the lymph nodes. (C). Dry pelvis with pins located at the position of the lymph nodes as determined from roentgenograms. (Reproduced with permission of *Radiology*.⁸)

to the pelvic walls and with efficient techniques survival rates were further improved.^{11,22} In some institutions 800 kv. or one million volt units were used.^{5,16}

Since World War II, 2 mev. roentgen-ray generators, kilocurie cobalt 60 units and 15 to 25 mev. betatrons have been used extensively in the management of cancers of the uterine cervix. More radical and efficient radium techniques also have been devised.^{17,18}

STAGING AND SUBSTAGING

To determine which cases are suitable for primary intracavitary radium therapy, it has been found necessary to subdivide the Stage II cases of the international classification into Stage II_A, in which the disease is limited to the upper two thirds of the vagina and/or there is minimal involvement of the parametria and no massive involvement of the corpus, and Stage II_B in which there is still tumor-free space but the disease extends almost to the pelvic walls or there is a "barrel-shaped" uterus on rectopelvic examination (Fig. 3).

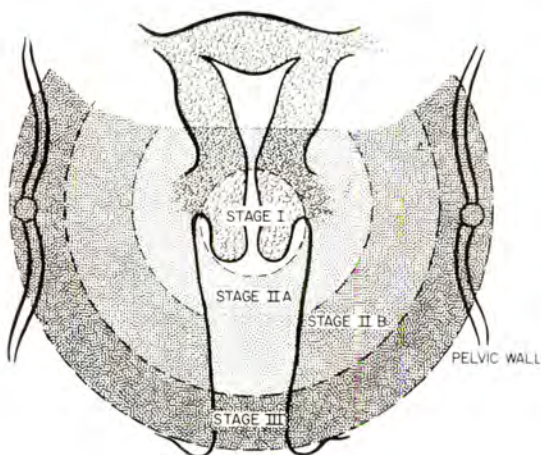


FIG. 3. Classification of carcinomas of the uterine cervix. Stage I_A, lesion less than 2 cm. in diameter; Stage I_B, lesion greater than 2 cm. in diameter, but still limited to the cervix; Stage II_A, involvement limited to the vagina and/or slight parametrial involvement; Stage II_B, involvement of the lateral aspects of the parametrium, with or without vaginal involvement; Stage III_A, involvement of one pelvic wall or the lower third of the vagina; Stage III_B, involvement of two pelvic walls or of one pelvic wall and the lower third of the vagina.

A survey of the literature¹² shows that the incidence of involvement of the pelvic wall lymph nodes is less than 25 per cent in Stage I and Stage II_A, around 40 to 50 per cent in the Stage II_B, and above 60 per cent in Stage III cases.

In the Stage I and Stage II_A cases, the emphasis should be on the local disease which can be encompassed within the intracavitary radium therapy zone of adequate dosage, but from Stage II_B on, the disease is beyond the reach of effective intracavitary radium therapy.

Following Garcia's¹¹ concept, the Stage III cases have been subdivided into Stage III_A, when only one pelvic wall is involved, and Stage III_B when both pelvic walls or one pelvic wall and the lower one third of the vagina are involved. The Stage III_B cases are those with frozen or near frozen pelvis and their prognosis is significantly worse than the prognosis of the Stage III_A cases.

The Stage IV cases are subdivided into those in which the disease is limited to the pelvis, usually with invasion of the bladder, and those with distant metastases. In the first group radical radiation therapy is still indicated.

THERAPEUTIC POSSIBILITIES OF SUPER-VOLTAGE IN CANCERS OF THE UTERINE CERVIX

There are essentially three ways of using supervoltage roentgen therapy:

1. *Supervoltage substituted for conventional voltage.* The same technique of intracavitary radium is used with external radiation to the lateral parametria and pelvic walls.^{4,22}

Blomfield⁴ has reported an increase in survival rates for all stages from 31 to 41 per cent for the same composition of clinical material. He has also found improvement within stages.

2. *External irradiation alone.* There are only small series of cancers of the cervix treated by external irradiation alone. Baclesse¹ irradiated some selected cases with 200 kv. More recently there have been attempts to control cervical cancers with

supervoltage roentgen therapy only. Tumor doses of 6,000 to 7,000 r have been given in six to seven weeks.^{3,20,21,25} The series is small and the information is fragmentary, but it seems that these doses are not sufficient. Watson and Burkell^{27,28} have effectively treated, with a 22 mev. betatron, a small number of Stage III and Stage IV cases with 7,500 to 8,000 r in five weeks.

3. *Whole pelvis irradiation followed by intracavitary radium therapy.* This technique is used in several institutions.^{13,14} It is the technique which has been utilized in our institution for the late Stage II, Stage III, and Stage IV cases.⁹ The rationale is that the site of origin of a tumor, which has been longest in existence, has a poor vascular supply and tumor cells are less radiosensitive. Therefore, to ensure control of the local disease, it is necessary to add local intracavitary radium therapy.

POLICIES OF TREATMENT SINCE THE AVAILABILITY OF SUPERVOLTAGE

Intracavitary radium therapy, carefully avoiding cold spots in the vicinity of the cervix, can encompass the local disease and its immediate extensions. Therefore:

1. The Stage I and Stage II_A cases are effectively treated by intracavitary radium therapy, provided the anatomy is suitable and there is no associated condition such as pregnancy or postpartum.

2. The Stage II_B and Stage III_A cases, because of involvement of the lateral parametria and the high incidence of pelvic wall nodes, are to be considered as generalized pelvic disease, with massive central disease. The emphasis is shifted to high dose whole pelvis irradiation with diminished local radium therapy.

3. The Stage III_B and Stage IV cases limited to the pelvis are in essence frozen pelvis and local additional therapy is often not indicated.

Table I summarizes the treatment policies.

RADIUM THERAPY AND DOSIMETRY USED IN OUR INSTITUTION

The intracavitary radium therapy is a

modification of the Manchester technique (Fig. 4).

The contribution from the radium system to the parametria and pelvic wall lymph nodes depends upon several factors

1. The total number of milligram hours (mgh).

2. The respective loading of the tandem and colpostats.

3. The location of the radium system within the pelvis.

Direct measurements^{7,10,26} have shown that the uterine radium is the main contributor to the pelvic wall lymph nodes because of its more central location within the pelvis. The contribution from the vaginal radium depends considerably upon the location of the radium system; this varies with age and distortion caused by



FIG. 4. Applicators used in intracavitary radium therapy. From left to right: dummy plastic ovoids used for fitting, plastic or rigid tandems of different lengths, various types of flanges, plastic jackets, metal ovoids with handles and vaginal cylinders. The ovoids are 2 cm. in diameter; 2.5 and 3 cm. ovoids are made by the addition of plastic jackets. The standard loading is, for the tandem, 15-10-10 mg. or 15-10 mg. and for the small, medium and large ovoids, respectively, 15, 20, 25 mg. If a protruding 10 mg. source is used because of separation of the vaginal sources, each ovoid loading is diminished by 5 mg. If there is any evidence of endometrial involvement (proved by positive endometrial biopsy of "barrel-shaped" uterus on rectopelvic examination), or if the disease originated in the endocervix or it is an adenocarcinoma, the radium content of the tandem is increased to 15-15-10, 20-15-10, or 15-15-20-15 mg. depending on the length of the uterine cavity. The vaginal radium is usually diminished by the same amount with which the uterine radium is increased.

TABLE I
POLICY OF TREATMENT IN CARCINOMAS OF THE UTERINE CERVIX

Stage	Treatment*	Exceptions
I	8,000–12,000 mgh in 2–4 insertions in 2–4 weeks, and 3,000–4,000 rads to parametria and pelvic walls	If lesion on cervix is large, 2,000–4,000 rads are given first to the whole pelvis in order to secure optimal geometric conditions for intracavitary radium therapy In case of associated pregnancy, or up to 1 year postpartum, 4,000 rads are given to the whole pelvis because of increased probability of metastatic disease in the pelvic wall lymph nodes
IIA	Same as Stage I	Same as Stage I
IIB	4,000 rads to the whole pelvis in 4 weeks with the betatron, followed by 4,500–6,500 mgh† in 2 insertions in 2 weeks	For adenocarcinomas and some selected cases of particularly infiltrative stony hard squamous cell carcinomas in Stage IIA, less whole pelvis radiation may be given in order to give more local radium therapy. A hysterectomy is performed in the adenocarcinomas and also in the large endocervical squamous cell carcinoma if regression is slow
IIIA	6,000 rads to the whole pelvis in 6 weeks with the betatron, followed by 4,000–5,000 mgh in one insertion‡	Same as Stage IIB
IIIB	7,000 rads to the whole pelvis in 7 weeks with the betatron occasionally with additional 2,000–3,000 mgh of radium‡	

* There are many adaptations: e.g., if there is extensive vaginal involvement, more vaginal radium is used, possibly a cylinder or interstitial needling. Irrespective of the total dose, 200 rads of tissue dose are given 5 days/week, i.e., 1,000 rads/week.

† The treatment time for 5,000 to 6,000 mgh of radium is between 40 and 48 hours for each insertion, usually a week apart (2 weeks apart if some intolerance develops, or if more shrinkage of the primary lesion is needed).

‡ In Stage III cases, a long protruding tandem is often used, as the vault is shrunken and can only accommodate a single ovoid. The tandem is dumbbelled (e.g., 20–15–15–20 mg.) with 1½ sources protruding and stays approximately 72 hours. Frequently, 500 to 1,000 rads are added on the involved side of a Stage IIIA case, with a 10 by 6 cm. portal.

The last 1,000 rads to the whole pelvis in Stages IIIB and IV are given through 2 parallel opposed portals, 12 by 12 cm.

disease (Fig. 5). In younger patients with roomy and distensible vaults, the radium is placed high in the pelvis; in older patients and also in patients with the vagina extensively involved by disease, the vagina is shorter and, therefore, the radium system is placed much lower. With a high location within the pelvis, the contribution to the obturator lymph nodes is approximately 1,000 r for each 4,400 mgh. The contribution to the hypogastric and external iliac lymph nodes is approximately half of that delivered to the obturator lymph nodes.⁷ In the best circumstances, the radium delivers a maximum of 2,000

r (9,000 to 10,000 mgh) to the obturator lymph nodes, and 1,000 r to the external iliac and hypogastric lymph nodes.

Doses to point A and point B of the Manchester school have been calculated but have not been used as a guide in our planning of treatment for individual cases or as a guide for the combination with external irradiation. Point A is theoretically at the crossing of the uterine artery and the ureter, but is not, as a rule, superimposed on any definite pelvic structure. This has been demonstrated by careful three dimensional studies.¹⁹ Point B is superimposed on the obturator lymph node,

which is one node among many, only when the radium system is located high in the pelvis.

The dosimetric procedures and the analysis of complications in correlation with the doses have been published.¹⁰

Direct measurements give information only to the level of the posterior fornix and slightly higher if a curved probe is used. The doses to the rectosigmoid and sigmoid vary with the location of the uterus within the pelvis. If the radium system is high and close to the sacrum, doses will be high and it would be of value to be able to determine them.

The uterine radium contributes most to the small intestine because the loops are wrapped around the uterus. In the absence of adhesions, the loops change position so that no one segment of small intestine is repeatedly irradiated. Pelvic surgery or inflammatory disease binds the small intestine by adhesions and greater care must be exercised in those cases.

The dose on a sphere of an arbitrary

radius of 7 to 8 cm., concentric with the center of gravity of the radium system could be a useful guide. This dose would be obtained by dividing the number of milligram hours by the inverse of the square of a constant radius and is tantamount to speaking in terms of milligram hours. The radium system should be weighted because the uterine radium contributes more radiation to the sigmoid and small intestines.

WHOLE PELVIS TECHNIQUE WITH SUPERVOLTAGE

Whole pelvis irradiation prior to radium therapy aims both to shrink disease on and around the cervix and to irradiate pelvic wall lymph nodes.

With a vaginal caliper, the projections of the cervix on the anterior and posterior surfaces of the abdomen are determined and the lower margin of the portals is marked accordingly.^{6,8} If there is involvement of only the cervix and the fornices the lower margin is set 4 cm. below the projection of the cervix. If the vagina is extensively involved, the rod is placed against the lowest palpable diseased area and the lower margin of the portal is marked to show four rings. The adequacy of coverage is checked by roentgenograms taken while the vaginal rod is in position counting the number of brass rings. As the height of the portals is always 15 cm. even if the involvement in the vagina is low, the coverage of the hypogastric lymph nodes may be marginal.

Two parallel opposed portals can be used for whole pelvis irradiation up to 4,000 or even 5,000 rads with a kilocurie cobalt 60 unit, 2 mev. roentgen-ray generator, or 22 mev. betatron.

It might be unwise to deliver, with two parallel opposed portals, 6,000 rads with a 2 mev. or kilocurie cobalt 60 unit since higher doses are delivered to the subcutaneous and muscular tissues. With a 22 mev. betatron, two parallel opposed portals could be used, but a four-field technique of anterior, posterior and two lateral

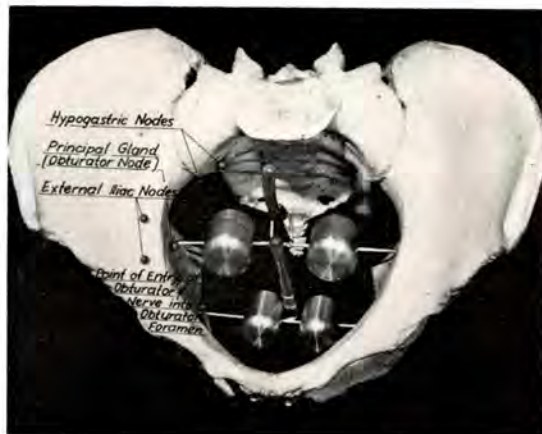


FIG. 5. Variations in location of the radium system within the pelvis. Small markers have been pinned on a bony pelvis to identify lymph node groups according to lymphadenectomy findings. Two actual radium systems have been reconstructed in space, showing the difference in relationship to the pelvis and lymph nodes. The lower radium system was used in the treatment of an elderly patient with a short, narrow vagina. The upper radium system was used in the treatment of a young patient with a roomy, distensible vagina.

portals produces an optimal volume distribution (Fig. 6).

The tissue doses are very homogeneous and therefore can be determined by calculating the dose at the center of the pelvis from depth dose tables. Daily settings can be accurately performed with simple accessories.

Attempts were made to deliver 6,000 rads on the pelvic walls at the rate of 1,000 rads per week with 360 degree rotation on the cobalt 60 unit. Excessive diarrhea developed because of the large volumes of intestines which receive doses of the order of 5,000, 4,000 and 3,000 rads. Using equi-arc rotation techniques, better tolerance is apparently obtained because the isodose curves are flattened anteriorly and posteriorly.^{20,21}

PARAMETRIAL TECHNIQUE WITH SUPERVOLTAGE

Two parallel opposed portals, with shielding centrally or asymmetrically located depending upon the volume distribution from the radium system, are used. The portals are 15 by 15 cm. and are checked by verification roentgenograms. In this instance, only the bony pelvic structures are of concern. The lower margin of the anterior and posterior portals transects the obturator foramen.

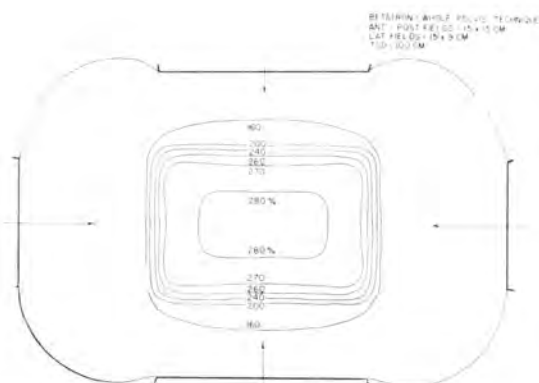


FIG. 6. Anteroposterior, posteroanterior and lateral portal technique with the 22 mev. betatron. The volume distribution is very homogeneous and the tumor dose can be calculated from depth dose at the center of the pelvis.

Central lead strips on the surface of the body produce, in the average patient, 1 cm. wider screening at mid-pelvis. The width of the shielding for the parametrial treatment ranges from 3 to 5 cm., depending upon the width of the zone of effectiveness of the radium system. The width is sometimes increased by steps to dovetail with the decrease of the lateral fall-off from the radium.

WEEKLY DOSAGE

With 15 by 15 cm. portals, 1,000 rads per week are well tolerated. Half of the patients have no symptoms, approximately 30 per cent have mild symptoms, and the remaining 20 per cent of the patients need some medication, such as bismuth and paregoric. Treatment is rarely discontinued because of excessive diarrhea. There are usually no bladder symptoms and, if present, are never severe unless there is pre-existing cystitis.

CARCINOMAS OF THE CERVICAL STUMP

The squamous cell carcinomas and the occasional adenocarcinomas of the cervical stump require adaptation of the methods of treatment because the absence of a uterine cavity diminishes the effectiveness of the radium therapy in the paracervical areas. Also, disease at the top of the remaining cervical canal is inadequately irradiated by the vaginal radium and the one source located in the remaining cervical canal. Therefore, whole pelvis irradiation is resorted to sooner than for the same stage of the disease on an intact uterus (Table II).

LARGE ENDOCERVICAL CARCINOMAS

There is a clinical variety of squamous cell carcinoma, or occasionally adenocarcinoma, originating apparently in the endocervix which produces extremely large tumors, sometimes 8 to 10 cm. in diameter. They may extend, on rectopelvic examination, almost from one side to the other of the pelvis, at times rendering difficult an appraisal of the parametrial situation.

In these cases if, after 4,000 rads and the

TABLE II
POLICY OF TREATMENT IN SQUAMOUS CELL CARCINOMAS OF THE CERVICAL STUMP*

Lesion	Treatment
Stage I	
Early	Vaginal radium and an endocervical source (25 mg.) for 72 hour and 3,500 rads transvaginally.† If endocervical canal is absent omit radium and increase transvaginal therapy to 6,000–7,000 rads
Moderately advanced with adequate vault. If vault is narrow, treated the same as Stage II advanced	Whole pelvis irradiation of 2,000 rads followed by intracavitary radium for 48 hours and transvaginal therapy of 3,500 rads with additional 2,000 rads to parametria.† If endocervical canal is absent omit radium and increase transvaginal therapy to 5,000 rads
Stage II	
Early	Same as moderately advanced Stage I stump lesion
Moderately advanced‡	Whole pelvis irradiation of 4,000 rads followed by intracavitary radium (2×48 hours) or transvaginal therapy of 4,000–5,000 rads
Advanced or massive‡	Whole pelvis irradiation of 6,000 rads followed by intracavitary radium for 72 hours or transvaginal therapy of 3,000–3,500 rad
Stage III	
All cases‡	Same as advanced Stage II stump lesion
Stage IV	
All cases	6,000 or 7,000 rads (last 1,000 rads with 12 by 12 cm. anteroposterior portal) to the whole pelvis

* With a long stump after a previous fundectomy, treatment is performed as if the uterus were intact (see Table I). With a short stump, the principle of treatment is to use the whole pelvis technique one stage sooner than in cases with intact uterus, because of less adequate radium system.

† Transvaginal therapy (usually with 140 kv., 3 mm. Al HVL) precedes radium therapy if the canal is long enough for radium source; otherwise, the radium precedes the transvaginal therapy.

‡ In patients with a narrow vagina and where the canal cannot be found, volume radium needling is used in place of transvaginal therapy or intracavitary radium. The doses are 3,000 to 5,000 rads depending upon the dose to the whole pelvis and the size of the volume implanted.

first radium insertion, there has not been regression of the fundus and cervix to normal size, a hysterectomy is performed. The second radium insertion is limited to give a maximum 5,500 mgh. The purpose of the hysterectomy is to eradicate residual disease in the myometrium.

ADENOCARCINOMAS

The adenocarcinomas of the cervix fall into 2 categories: (1) those which, after fractional curettage, are shown to be limited to the cervix, and (2) those with positive endometrial biopsy, which are allotted, according to Heyman's classification, to the corpus et collum category.

The adenocarcinomas limited to the

cervix are essentially managed like the squamous cell carcinomas; however, because of their reputation of less radiosensitivity, there is a tendency, in the Stage II_A and Stage III cases to give smaller doses of whole pelvis radiation and to use more intracavitary radium therapy. For instance only 2,000 rads may be delivered to the whole pelvis in a Stage II_B case, with correspondingly heavier intracavitary radium therapy. In Stage I and Stage II_A, and Stage II_B cases, a hysterectomy and lymphadenectomy are performed, the radiation therapy being slightly less radical.

The corpus et collum adenocarcinomas are managed like cervical adenocarcinomas provided a hysterectomy can be performed

if the disease is too advanced or there are medical contraindications, vaginal ovoids with the same radium dosage as for the cervical cancers, combined with the Heyman's packing technique (2,500 mgh of radium for each insertion), are utilized. Longer fractionation is used and the packing may be repeated three times, with two weeks between each.

In summary, the policy for the treatment of patients with adenocarcinomas of the cervix is to combine radium therapy, effective in irradiating the vaginal sheath and paracervical areas, with a hysterectomy which removes the residual disease in the uterus.

CARCINOMA OF THE CERVIX ASSOCIATED WITH PREGNANCY OR THE POSTPARTUM PERIOD

The results in cases of squamous cell carcinomas of the uterine cervix associated with pregnancy or diagnosed up to one year postpartum, analyzed in 1954 when supervoltage became available, showed:

1. That the cure rate was significantly lower than the cure rate of other cases (11 dead of 22 patients treated for Stage I and Stage II). Many deaths occur within one year and almost all (93 per cent) within two years.

2. That the influence of pregnancy on cure rate was felt up to one year postpartum (of 15 treated for disease with symptoms starting 7 to 12 months after delivery, 10 patients died).

3. That a small series of lymphadenectomies suggested a higher incidence of involvement of pelvic wall lymph nodes than in the cases not connected with pregnancy or postpartum, indicating an increased metastatic aggressiveness.

It was decided to give to the Stage I and Stage II cases a dose of 4,000 rads to the whole pelvis. The rest of the treatment is adapted to the clinical situations.

In the first trimester of the pregnancy, abortion usually occurs after 2,000 to 3,000 rads are given. When external irradiation is completed at four weeks, the usual

intracavitary radium therapy can be used.

In the second trimester, abortion usually occurs before 4,000 rads are delivered. When external irradiation is completed, the uterus has involuted enough to proceed with the normal radium therapy. There have been 4 instances in which abortion did not occur by the time 4,000 rads had been delivered. In those cases vaginal radium only was used and a hysterectomy performed.

In the third trimester, if the fetus is viable, a high cesarean section is done and whole pelvis irradiation is started three or four days afterward. The uterus is sufficiently involuted after 4,000 rads are delivered to carry the normal intracavitary radium therapy. A more complex problem is present when the patient is six to seven and one-half months pregnant. A decision must be made whether or not to postpone treatment until survival of fetus is probable.

In the immediate postpartum period 4,000 rads are given to the whole pelvis. The uterus is fully involuted at the end of the external irradiation and radium therapy can be performed without difficulty. The worst results are in patients who have delivered through a diseased cervix.

LYMPHADENECTOMY STUDIES

The effectiveness of 4,000 or 6,000 rads whole pelvis irradiation plus the contribution from the radium system on metastatic pelvic wall lymph nodes can be evaluated only by an anatomic and histologic study.

The results of lymphadenectomies in unselected cases have been published.²⁴ Further studies (Table III) have confirmed that the incidence of positive pelvic wall lymph nodes is around 20 per cent in Stage III cases. This is much less than the expected 60 to 70 per cent according to the literature.¹²

There is a relatively higher incidence of involved pelvic wall lymph nodes in Stage II_B cases. This indicates that 4,000 rads plus the contribution from 5,500 to 6,000 mgh of radium, which is at most 1,500 r

TABLE III
340 LYMPHADENECTOMIES IN UNSELECTED
SQUAMOUS CELL CARCINOMAS ON
INTACT UTERUS
1955-1960

Stage	Lymphaden- ectomies	Per Cent of Patients with Positive Pelvic Wall Lymph- Nodes
Stage I	41	2.5 (1)*
Stage II _A	64	8 (5)
Stage II _B	59	20 (12)
All Stages II	129	13 (17)
Stage III _A	85	17 (14)
Stage III _B	85	22 (19)
All Stages III	170	19 (33)

* () number of cases.

One hundred consecutive Stage III cases were subjected to lymphadenectomies. Following the completion of this series, using a randomization scheme, lymphadenectomies were performed on patients with Stage I to III_B disease.

The lymph nodes around the bifurcation of the common iliac artery into the hypogastric and external iliac arteries are included in the "hypogastric nodes" group.

to the obturator lymph nodes and 700 r to the other lymph node areas, may not be as effective as 6,000 rads plus the contribution of 4,000 to 5,000 mgh of radium.

There is a high incidence of positive periaortic lymph nodes in the cases in which pelvic wall lymph nodes are positive. The explanation is that radiation fails to control the larger metastatic nodes (larger tumor masses are less radiosensitive), and that the next lymphatic relays are more often involved with massive metastases to the proximal lymphatics.

RESULTS OF TREATMENT

The material analyzed consists of all cases of cancers of the uterine cervix, where the primary was untreated, registered from August, 1948, through August, 1958.

From August, 1948, through August, 1954, a 400 kv. unit was used for external irradiation. Since September, 1954, a 22 mev. betatron has been employed almost exclusively.

The material is subdivided (Table IV)

into squamous cell carcinomas on the intact uterus, stump carcinomas, and adenocarcinomas limited to the cervix. The incidence of Stage I and Stage II_A cases combined is the same in the presupervoltage and supervoltage series. There is a slight shift to more Stage III_B and Stage IV cases being treated because after the availability of a supervoltage roentgen therapy unit, attempts were made to treat, more often and more systematically, the very advanced cases. This has been found to be only slightly rewarding.

In the two series the distribution by economic strata is not different; both are composed almost entirely of charity cases. Approximately 50 per cent of the patients in the presupervoltage series were Negro and Latin American (more advanced cases), while the percentage is 40 per cent in the supervoltage series. The age distribution of the two groups is similar.

Table v gives the survival rates for the three categories: squamous cell carcinomas on the intact uterus, stump carcinomas, and adenocarcinomas. There is an apparent improvement in survival rates in the Stage II_B, Stage III_A, and Stage III_B cases of the supervoltage series. The survival rates in Stage IV are relative to the percentage of cases treated, which is at most 40 per cent of all Stage IV cases registered.

The results in the pregnancy or postpartum cases are much improved. The improvement is the same for the two groups of cases—pregnancy up to six weeks postpartum and six weeks postpartum to one year. The increased survival rate is most marked for Stage I cases (all 18 patients treated are still alive).

An analysis of the sites in which the failures occurred in Stage I through Stage III_A cases reveals a shift in the cause of death from pelvic disease to distant metastases or intercurrent diseases (Table VI). In Stage III_B there is the same proportion of pelvic disease failures, emphasizing that in these massive cancers there is still uncontrolled local disease producing death before distant metastases become manifest.

TABLE IV

ALL CASES OF CANCER OF THE UTERINE CERVIX

Presupervoltage—August, 1948 to September 1, 1954; Supervoltage—September 1, 1954 to September 1, 1958

Stage		Intact Uterus		Stump		Adenocarcinoma	
		Presuper-voltage	Since Supervoltage	Presuper-voltage	Since Supervoltage	Presuper-voltage	Since Supervoltage
I	Treated Untreated Total	64 0 64	117 1 118	7 0 7	7 0 7	1 0 1	6 1 7
IIA	Treated Untreated Total	129 0 129	106 2 108	14 0 14	14 0 14	4 0 4	6 0 6
IIB	Treated Untreated Total	123 2 125	114 1 115	15 1 16	6 0 6	4 0 4	6 0 6
All Stages II	Treated Untreated Total	252 2 254	220 3 223	29 1 30	20 0 20	8 0 8	12 0 12
IIIA	Treated Untreated Total	93 5 98	130 8 138	5 0 5	7 0 7	2 0 2	5 0 5
IIIB	Treated Untreated Total	87 23 110	148 11 159	4 2 6	15 2 17	1 1 2	4 0 4
All Stages III	Treated Untreated Total	180 28 208	278 19 297	9 2 11	22 2 24	3 1 4	9 0 9
IV	Treated Untreated Total	19 44 63	37 47 84	1 3 4	2 5 7	0 1 1	0 1 1
Total	Treated Untreated Total	515 74 589	652 70 722	46 6 52	51 7 58	12 2 14	27 2 29

TREATED SQUAMOUS CELL CARCINOMAS OF THE CERVIX, INTACT UTERUS
Percentage of Each Therapeutic Group

	Stage I and IIA	Stage IIB	Stage IIIA	Stage IIIB	Stage IV
Presupervoltage	35.5	23.9	18.1	16.9	3.7
Supervoltage	34.0	17.5	20.0	22.7	5.7

The therapeutic groups, consisting of Stage I and Stage IIA combined, Stage IIB, Stage IIIA, Stage IIIB and Stage IV, form the main therapeutic divisions. There is no appreciable difference in the distribution of the orthovoltage and supervoltage material by therapeutic groups.

A few patients in the Stage I, Stage II, and Stage IIIA groups were not treated because they refused treatment or because of some associated condition (insanity, other cancer, other disorders) which prevented treatment.

There is a greater proportion of untreated cases in the Stage IIIB group prior to supervoltage therapy because little could be achieved with conventional voltage in patients with frozen pelvis or bilaterally blocked kidneys. Since the availability of supervoltage therapy, a more systematic attempt to control frozen pelvis has been made, but it has been found that the results are still not encouraging in patients with bilaterally blocked kidneys or in very elderly patients.

The squamous cell carcinomas of the stump in the supervoltage group have a greater proportion of Stage III cases.

The two groups of adenocarcinomas, few in number, have about the same distribution.

TABLE V
TREATMENT RESULTS
ALL PATIENTS TREATED FOR CARCINOMA OF THE UTERINE CERVIX
August, 1948–August, 1958

Stage	Before Supervoltage 1948–September, 1954		Supervoltage 1954–September, 1958	
	No. Treated	Per Cent Survived 5 Yr.	No. Treated	Per Cent Survived 5 Yr.
ALL SQUAMOUS CELL CARCINOMAS ON INTACT UTERI*				
I	64	90 (± 3.6)*	117	93 (± 2.4)*
IIA	129	80 (± 3.5)	106	83 (± 3.9)
IIB	123	60 (± 4.4)	114	73 (± 4.2)
All Stages II	252	70 (± 2.9)	220	78 (± 3.0)
IIIA	93	44 (± 5.3)	130	56 (± 4.7)
IIIB	87	31 (± 4.9)	148	38 (± 4.2)
All Stages III**	180	37 (± 3.6)	278	46 (± 3.2)
IV	19	5 (± 5.1)	37	14 (± 6.4)
All Stages	515	59 (± 2.2)	652	63 (± 2.0)
PREGNANCY AND UP TO ONE YEAR POSTPARTUM***				
All Stages	30	40.5 (± 9.2)	44	55.5 (± 6.4)
SQUAMOUS CELL CARCINOMAS OF STUMP†				
All Stages	46	61 (± 7.2)	51	63 (± 8.9)
ADENOCARCINOMAS††				
All Stages	12	50 (± 14.4)	27	85 (± 7.1)

* (\pm) Standard error. Prepared, according to Berkson-Gage method, by Mary C. Macdonald, Biometrician in the Section of Radiotherapy.

** The greatest increase in survival rate is in the Stage III cases. The survival rates for Stage I, IIA and Stage IV cases are relatively unchanged.

About 30 per cent of the Stage IV intact uterus cases in the presupervoltage series were considered worth treating, whereas approximately 45 per cent of the Stage IV cases were treated in the supervoltage series. The absolute survival rate in Stage IV cases with intact uterus is 1.5 per cent in the presupervoltage series and 8 per cent in the supervoltage series.

There are two possible reasons for the apparent discrepancy between the increase in survival rates for each stage and the over-all survival rates: 1) 14.5 per cent of the patients in the presupervoltage series were not treated, compared with 11 per cent in the supervoltage series; 2) to move the percentage from 59 to 64 means salvage of 5 patients in 40, and these are contributed by the segment of moderately advanced cases, i.e., the Stage IIB and Stage IIIA cases, which are most benefited.

*** The pregnancy and postpartum cases are included in the group of squamous cell carcinomas on intact uteri.

† There is no difference in survival rates for all stages of the stump carcinomas. The proportion of Stage III cases is greater in the supervoltage group.

†† The improvement in survival rates for the small group of adenocarcinomas in the supervoltage group may be partially attributed to the fact that hysterectomies had been performed when possible.

TABLE VI

SITES OF ACTIVE DISEASE PRIOR TO DEATH IN SQUAMOUS CELL CARCINOMAS ON INTACT UTERI

Presupervoltage—August, 1948 to September 1, 1954; Supervoltage—September 1, 1954 to September 1, 1958

Stage	No. Dead of No. Treated		V Alone	V +PD	V +PD +DM	V +DM	PD	PD +DM	DM	ID	Com- plica- tions	No Data
	Presuper- voltage	Super- voltage										
I and II _A	41/193		0	6	4	1	9	5	5	4	1	6
		23/175	0	2	0	0	1	1	8	8	1	2
II _B	50/123		0	3	4	0	19	6	7	4	2	5
		27/89	0	1	2	1	5	3	9	6	0	0
III _A	54/93		0	12	3	0	17	4	5	4	0	9
		27/89	0	9	3	0	5	8	10	7	4 (necr)	3
III _B	63/87		0	28	6	0	15	6	1	1	0	7
		72/117	0	21	8	0	14	4	7	4	4 (necr)	10
IV	18/19		0	4	2	0	3	1	3	0	0	5
		25/30	0	7	11	0	0	1	4	1	1 (necr)	0

The supervoltage group to the end of 1957 had a follow-up of a minimum of three years. As few patients die between three to five years, this series can be used for analysis of trends in distribution of sites of active disease.

The evaluation of sites of active disease is mostly clinical, occasionally based on surgical or autopsy findings. The patients listed under the column of no data are those who, when last seen, were without evidence of disease and who died at some later date without any reliable information as to status prior to death.

Disease on the vault (V) is local disease in the vagina or the remaining uterus.

Pelvic disease (PD) means active disease outside of the vagina or the remaining uterus, almost always pelvic wall disease.

Only uncontroversial distant metastases (DM) are counted. Lung metastases seen on roentgenograms are most frequent, followed by supraclavicular lymph node and bone metastases.

The shift to distant metastases and intercurrent disease (ID) is evident in Stages I, II_A, II_B, and III_A.

In the Stage III patients who have died, the cause of death has been most often pelvic disease or even pelvic disease and local disease in the presupervoltage and supervoltage series.

The necroses (necr) of small bowel which produced death were all in the lymphadenectomy group.

DISCUSSION

An evaluation of supervoltage roentgen therapy compared with conventional methods depends, of course, upon the results prior to the use of supervoltage. Radical radium therapy combined with external irradiation can produce higher than 50 per cent survival rates.^{17,18}

The improved survival rates in Stage II_B, Stage III_A, and Stage III_B are probably

significant. This is further substantiated by the fact that the lymphadenectomy series has demonstrated a high incidence of sterilization of pelvic wall disease.

The results with conventional techniques are obtained with a high degree of individualization and elaborate radium therapy. This is hard to maintain when a larger group of treating physicians is involved. It is also hard to duplicate in other clinics.

High dose whole pelvis irradiation of

4,000 rads in bulky lesions and Stage II_B cases and of 6,000 rads in Stage III cases has simplified treatments. Individualization, still necessary for the additional intracavitary radium therapy is not nearly as elaborate. A hysterectomy with lymphadenectomy can be performed when indicated without undue risk of complications.

The severe complications almost always occur in the patients having received 6,000 rads and additional surgery. Sigmoiditis of various degrees of severity is the only complication inherent to high dose whole pelvis irradiation.

It must be emphasized that these results, both in cure rates and complications, are derived from a specific technique with a 22 mev. betatron, which, because of the use of lateral portals, produces minimum

irradiated volumes.

As the incidence and severity of complications due to high dose whole pelvis technique are better established, it is conceivable that all cases, with the exception of very early Stage I, will be given 4,000 rads to the whole pelvis, and 6,000 rads will be reserved for late Stage III cases, unless the anatomy precludes satisfactory radium therapy.

The cases having had 7,000 rads or 8,000 rads with or without some additional radium were mostly of Stage III_B and Stage IV. Twelve out of 49, *i.e.*, approximately 25 per cent, are living two years or more (Table VII), showing that there is some value in treating very radically massive cancers. Of the 37 patients dead, 27 died with pelvic disease and three others died

TABLE VII
PATIENTS TREATED WITH HIGH DOSE WHOLE PELVIS IRRADIATION
September 1, 1954 to March 1, 1959

Treatment	Stage	Total No.	No Evidence of Disease 2 to 6 yr.	Pelvic Disease	Distant Metastases	Other Causes
7,000 rads plus radium	III _A	1	1	0	0	0
	III _B	11	3	7	1	0
	IV	4	0	4	0	0
8,000 rads plus radium	III _A	1	0	1	0	0
	III _B	9	1	5	2	1 (necr)
	IV	2	1	0	0	1 (necr)
7,000 rads—no radium	III _A	2	1	1	0	0
	III _B	10	2	4	1	3
	IV	1	1	0	0	0
8,000 rads—no radium	III _B	5	1	3	0	1 (necr)
	IV	2	0	2	0	0
Totals		48	11	27	4	6

from necroses as a complication of their treatment.

CONCLUSIONS

Intracavitary radium therapy remains the best radiation method for permanent control of the early cancers of the uterine cervix.

Supervoltage roentgen therapy, in this instance a 22 mev. betatron, permits the systematic use of high dose whole pelvis irradiation in the treatment of bulky primary lesions, late stages of cancer of the uterine cervix and in the biologically more aggressive tumors associated with pregnancy or postpartum.

An extensive study of lymphadenectomies has demonstrated that metastatic disease and involved pelvic wall lymph nodes can be sterilized by irradiation.

The survival rates in the supervoltage series are above 60 per cent for all patients treated, and 55 per cent for all patients registered. The survival rates by stages are 90 per cent in Stage I, 75 per cent in Stage II, 40 per cent in Stage III, and only an occasional case is cured in Stage IV.

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COMPLICATIONS IN HIGH DOSE WHOLE PELVIS IRRADIATION IN FEMALE PELVIC CANCER *

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THE complications resulting from radium therapy, alone or combined with orthovoltage external irradiation, in the treatment of patients with squamous cell carcinomas of the uterine cervix have been extensively studied in world radiotherapy centers. Common complications such as vault necrosis, bladder and rectal ulcers, and vesico- and rectovaginal fistulae have been attributed to high doses to the surrounding structures. With the accumulation of clinical experience and the improvement of dosimetric methods, significant advances were achieved and in such large series as those of the Radiumhemmet⁴ few major complications are now seen. The literature pertaining to complications specific to supervoltage therapy is almost nonexistent.

The complications in the patients treated in our institution prior to the availability of supervoltage roentgen therapy have been reported previously and evidence has been given that careful dosimetric procedures, in particular direct measurements of bladder and rectal doses, resulted in fewer significant complications.¹

The availability of a 22 mev. betatron in 1954 brought about a radical change in the techniques for treatment of the more advanced cases. An extensive associated program of lymphadenectomies⁵ and a greater effort to eradicate recurrent or residual disease by total hysterectomies and/or exenteration has been carried out.

Concomitant with the initiation of supervoltage roentgen therapy in 1954, the permanent hospital was occupied. Although adequate facilities were available in the

previous temporary quarters, clinicians were not as free to carry out extensive investigations for minor symptomatology. This may explain the relative increase, since 1954, in the incidence of complications of less severity such as dysuria, proctitis, and moderate sigmoiditis.

The complications will be discussed in the following order: (1) proctitis, (2) rectal ulcer, (3) severe dysuria (radiation cystitis), (4) bladder ulcer, (5) sigmoiditis, (6) fistula, (7) small bowel necrosis, (8) vault necrosis, (9) excessive pelvic fibrosis with ureteral strictures, and (10) pelvic bone injury.

The material will be analyzed according to: (a) the type, relative incidence, and severity of complications comparing conventional versus supervoltage therapy (with particular reference to two main dose levels of 4,000 rads and 6,000 rads or more to the whole pelvis) combined with radium therapy; (b) the influence of lymphadenectomies and hysterectomies or exenterations on the complications in cases treated by conventional methods or with the two dose levels of 4,000 and 6,000 rads or more; and (c) the dose levels compatible with an additional surgical procedure. Although this study will review the complications in relationship to associated surgical procedures, the specific surgical complications will not be analyzed.

CLINICAL MATERIAL

The material consists of 741 patients treated between September 1, 1954 and March 1, 1959 for previously untreated squamous cell carcinomas of the uterine

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TABLE I
DISTRIBUTION OF CLINICAL MATERIAL
(September 1, 1954 to March 1, 1959)
(741 Patients)

Stage	No. of Patients	Irradiation Only	Postirradiation Lymphadenectomy	Postirradiation Hysterectomy or Exenteration* and Lymphadenectomy
I	130	94	31	5
IIA	127	82	32	13
IIB	130	75	35	20
IIIA	147	66	64	17
IIIB	165	92	58	15
IV	42	38	2	2
Total	741	447 (60.3%)	222 (30%)	72† (9.7%)

* There were 10 exenterations.

† In 43 per cent (31 cases) residual or recurrent carcinoma was found in the surgical specimen.

TABLE II
PATIENT DISTRIBUTION BY TREATMENT TECHNIQUE
(September 1, 1954 to March 1, 1959)
(741 Patients)

	Irradiation Only	Postirradiation Lymphadenectomy	Postirradiation Hysterectomy or Exenteration and Lymphadenectomy
Radium with/without Parametrial Irradiation			
Stage I	76	22	2
Stage IIA	45	16	9
Stage IIB	12	6	0
Stage IIIA	4	2	2
Stage IIIB	1	0	0
Stage IV	0	0	0
Total	138	46 (23.2%)	13 (6.6%)

(Table II continued in next column)

2,000 rads Whole Pelvis+Parametrial
Irradiation+Radium

Stage I	14	4	2
Stage IIA	29	11	4
Stage IIB	9	6	2
Stage IIIA	0	1	0
Stage IIIB	1	0	0
Stage IV	2	0	0
Total 85	55	22 (25.8%)	8 (9.4%)

4,000 rads Whole Pelvis Irradiation+Radium

Stage I	4	5	1
Stage IIA	5	4	0
Stage IIB	44	17	9
Stage IIIA	16	14	4
Stage IIIB	2	1	0
Stage IV	2	1	0
Total 129	73	42 (32.6%)	14 (10.8%)

6,000 rads or More Whole Pelvis Irradiation
with/without Radium

Stage I	0	0	0
Stage IIA	2	1	0
Stage IIB	10	6	7
Stage IIIA	43	47	11
Stage IIIB	81	57	15
Stage IV	22	1	2
Total 305	158	112 (36.8%)	35 (11.5%)

Incomplete Treatment:

25 Patients. (IIA—1 (no surgery)
IIB—2 (lymphadenectomy and hysterectomy)
IIIA—3 (no surgery)
IIIB—7 (no surgery)
IV—12 (no surgery; palliative treatment to 4,000 rads whole pelvis irradiation)

cervix. This provides a minimum two year period of observation which is adequate for the study of complications since, similar to the classic rectal complications, almost all the sigmoid and small bowel injuries occur within eight to fifteen months after therapy (occasionally, between fifteen to twenty-four months and, exceptionally, after two years).

Tables I and II show the distribution of the 741 patients by stage, treatment techniques, and surgical procedures.

There are more lymphadenectomies in the Stage IIIA and Stage IIIB groups (43 and

35 per cent respectively) than in the Stages I, II_A and II_B groups because, originally, lymphadenectomies were carried out on 100 consecutive Stage III cases and, later, on Stage I through Stage III cases with a randomized scheme.

Approximately the same number of hysterectomies and/or exenterations have been performed in the Stage II and Stage III cases. The exenterations, although included, compose a small number.

COMPLICATIONS

PROCTITIS

Cases listed under proctitis are those with symptoms of pain, intermittent diarrhea, tenesmus, and a small amount of rectal bleeding. The symptoms appear between six to thirteen months following treatment with the majority occurring between six to nine months. The duration of the symptoms is from four weeks to four months. Only in an occasional patient has blood transfusion and hospitalization been necessary because of persistent rectal bleeding.

In Table III the incidence of proctitis is tabulated by dose levels and surgical procedures. The 4,000 rads whole pelvis irradiation group is almost free from this complication. One patient who developed proctitis had had additional radium therapy because of extensive low vaginal disease.

There were 4 cases (approximately 1 per cent) of proctitis in the group of patients who received 6,000 rads or more whole pelvis irradiation.

Lymphadenectomies and/or hysterectomies do not add to the incidence of proctitis.

RECTAL ULCER

The symptoms of rectal ulcer are similar to those of proctitis except that they are more severe and more persistent. Without proctoscopy or roentgen examination, the diagnosis might be only one of proctitis.

The use of dosimetric procedures in the presupervoltage series had diminished the incidence of rectal ulcers. These same dosimetric procedures have been carried out since the availability of supervoltage. There is complete freedom from rectal ulcer in all

TABLE III

PROCTITIS

(September 1, 1954 to March 1, 1959)
(741 Patients)

Treatment	No. of Patients	Irradiation Only (447 cases)	Postirradiation Lymphadenectomy (222 cases)	Postirradiation Hysterectomy or Exenteration and Lymphadenectomy (72 cases)
Radium with/without Parametrial Irradiation	197	1-Stage I	0	0
2,000 rads Whole Pelvis Irradiation + Radium	85	0	0	0
4,000 rads Whole Pelvis Irradiation + Radium	129	1-Stage I*	0	0
6,000 rads or More Whole Pelvis Irradiation + Radium	305	4-Stage III _A Stage III _A Stage III _B Stage IV†	0	0

* Also had 5,000 r to the lower vagina by a radium implant.

† 8,000 rads whole pelvis irradiation + radium.

TABLE IV
RECTAL ULCER
(September 1, 1954 to March 1, 1959)
(741 Patients)

Treatment	No. of Patients	Irradiation Only (447 cases)	Postirradiation Lymphadenectomy (222 cases)	Postirradiation Hysterectomy or Exenteration and Lymphadenectomy (72 cases)
Radium with/without Parametrial Irradiation	197	0	0	0
2,000 rads Whole Pelvis+Parametrial Irradiation+Radium	85	0	0	0
4,000 rads Whole Pelvis Irradiation+Radium	129	0	0	0
6,000 rads or More Whole Pelvis Irradiation+Radium	305	3-Stage III _B * Stage III _B Stage III _B †	0	1-Stage II _B (II _B)††

* 8,000 rads whole pelvis irradiation.

† 7,000 rads + radium.

†† Included in ileosigmoid fistula count.

groups except in Stage III_B cases which received 6,000 rads or more whole pelvis irradiation (Table IV).

The time of appearance of rectal ulcers is between nine to twelve months; 1 case appeared at fourteen months. Self healing is the rule. One patient, treated with 7,000 rads, required a colostomy; roentgenograms showed that the tandem was situated low, close to the rectum. One case was also complicated with an ileosigmoid fistula. Another case, treated with 8,200 rads to the whole pelvis, was hospitalized for bleeding, but eventually healing occurred.

The addition of lymphadenectomy and/or hysterectomy does not contribute to the incidence of rectal ulcers.

DYSURIA

There is always some measure of dysuria during and shortly after irradiation. The cases included in this series are those with lasting discomfort. The symptomatology consists of spasm and frequency, hematuria, and occasionally ascending renal infection.

On cystoscopic examination there is evidence of radiation cystitis with or without superficial ulceration.

As in the presupervoltage series, in most of the cases dysuria has appeared between one to two years, usually before eighteen months. Table V shows that dysuria is closely related to the radium therapy; study of the therapy data revealed that the position of the radium system produced high doses to the bladder.

The symptoms have lasted intermittently from a few months to as long as three to four years. In the more severe cases, cauterization has been required to stop the bleeding.

One must note the freedom from this complication in the group receiving 4,000 rads whole pelvis irradiation; the only patient with dysuria in this group had had a definitely faulty positioning of the radium system. Dysuria is not a complication specific to 6,000 rads or more whole pelvis irradiation. The lymphadenectomy group seems to have a slightly higher incidence.

TABLE V
DYSURIA
(September 1, 1954 to March 1, 1959)
(741 Patients)

Treatment	No. of Patients	Irradiation Only (447 cases)	Postirradiation Lymphadenectomy (222 cases)	Postirradiation Hysterectomy or Exenteration and Lymphadenectomy (72 cases)
Radium with/without Parametrial Irradiation	197	3-Stage I* Stage I* Stage II _A *	2-Stage I Stage II _A	0
2,000 rads Whole Pelvis Irradiation + Parametrial Irradiation + Radium	85	0	1-Stage II _A *	0
4,000 rads Whole Pelvis Irradiation + Radium	129	0	1-Stage III _A *	0
6,000 rads or More Whole Pelvis Irradiation + Radium	305	1- Stage III _B (sigmoiditis)	1-Stage III _A	1-Stage III _A *

* Position of the radium delivered a high dose to the bladder.

BLADDER ULCER

Most bladder ulcers appear from six months to two years after therapy, but they can appear later.¹ In the present supervoltage series, 2 cases appeared at three and four years, respectively.

The symptoms are similar to those of dysuria, but hematuria is more persistent, at times profuse and difficult to control. Two cases have been associated with renal changes that resulted in a nonfunctioning kidney in 1 patient and pyelonephritis in another. The latter patient underwent a nephrectomy. Symptoms have been found to persist intermittently for an average of eight months; in 1 case symptoms lasted as long as two years.

The ulcers are commonly located in the trigone or slightly beyond, and only occasionally in the dome of the bladder. Treatment has been, as a rule, conservative; occasionally a patient required blood transfusion or cauterization of the ulcer to stop the bleeding.

Table VI shows the frequency of bladder ulcers caused by irradiation and surgical

procedures. Extreme ante flexion of the uterus, with resulting high doses to the bladder by the radium in the tandem, is the common cause in the Stage I cases which were treated by radium alone. The group of cases receiving 4,000 rads to the whole pelvis is free from bladder ulcers. Supplemental surgical procedures do not seem to increase the incidence of bladder ulcers.

SIGMOIDITIS

The diagnosis of sigmoiditis or proctosigmoiditis is made by a thorough evaluation of (a) clinical symptoms, (b) roentgenologic examination, and (c) proctosigmoidoscopic examination. It is only after this complete work-up that the diagnosis can be established and the severity of the case can be fully appreciated. Without complete proctoscopic and roentgenologic examination, the diagnosis remains uncertain despite a suggestive symptomatology. Repeated proctoscopic and roentgenologic examinations should follow the changes in the injured segment. There were cases in which symptoms developed so acutely that

surgical intervention was immediately necessary and the diagnosis was made from the operative findings.

The symptomatology consists of rectal bleeding, mucus discharge, abdominal cramps, pain on defecation, and alternate episodes of diarrhea and constipation. Depending upon the severity of the organic damage, the symptoms may either subside or recur over a long period of time. In the mild or moderately severe cases, rectal bleeding is usually slight and does not require particular attention. In the more severe cases bleeding may persist even after colostomy, causing anemia; fistulae can develop from continuing necrosis, and pelvic abscess can occur from perforation.

Based on the symptomatology and the roentgen findings, radiation sigmoiditis can be classified according to three degrees of severity: mild, moderate, and severe.

A. *Mild Sigmoiditis*. The symptoms are mild and temporary. Roentgen examination shows a spasm of the sigmoid and at rectosigmoidoscopic examination edematous changes in the mucosa are noted. The involved segment varies in extent but is

usually of short length. There is no real narrowing of the lumen except in the presence of spasm which may, in some cases, contribute to a low grade obstruction.

B. *Moderate Sigmoiditis*. The symptoms are the same as in mild sigmoiditis but they are more persistent and more severe, with occasional subacute intestinal obstruction. Gaseous distention is a frequent complaint. Surgical intervention is rarely indicated. A low residue diet, mineral oil and, occasionally, antispasmodics are adequate to control the symptoms, which tend to ease with time.

Roentgen examination shows a localized smooth concentric narrowing with loss of normal mucosal folds and distensibility. Occasionally, ulcerations may be demonstrated on roentgenograms but these are seen more often during sigmoidoscopy.

C. *Severe Sigmoiditis*. Barium study discloses a markedly narrowed segment and, in some instances, a complete obstruction. Surgical intervention is required in most cases to avoid low bowel obstruction. Occasionally, perforation may occur at the

TABLE VI
BLADDER ULCER
(September 1, 1954 to March 1, 1959)
(741 Patients)

Treatment	No. of Patients	Irradiation Only (447 cases)	Postirradiation Lymphadenectomy (222 cases)	Postirradiation Hysterectomy or Exenteration and Lymphadenectomy (72 cases)
Radium with/without Parametrial Irradiation	197	3-Stage I* Stage II _A Stage II _B	○	○
2,000 rads Whole Pelvis Irradiation + Parametrial Irradiation + Radium	85	○	1-Stage III _A *	○
4,000 rads Whole Pelvis Irradiation + Radium	129	○	○	○
6,000 rads or More Whole Pelvis Irradiation + Radium	305	2-Stage II _B Stage III _A *	1-Stage III _A	1-Stage III _B

* Position of the radium delivered a high dose to the bladder.

site of obstruction, producing abscesses or peritonitis.

There were cases with constrictive changes which were managed without a surgical procedure. On later examination the markedly constricted area had widened considerably because of decreased edema or physiologic compensation (Fig. 1, A-D).

The most severe form of sigmoiditis does not exhibit the regular pattern described

above. It is a diffuse, acutely extensive reaction or necrosis of a segment of the sigmoid. The symptoms are those of an acute abdomen rather than the insidious symptoms of bleeding or abdominal cramps. Roentgenograms show a long segment of the sigmoid marked by gross irregularities (distorted by destruction of mucosal patterns) coupled with ulcerations and irregular narrowing. It is in this group that

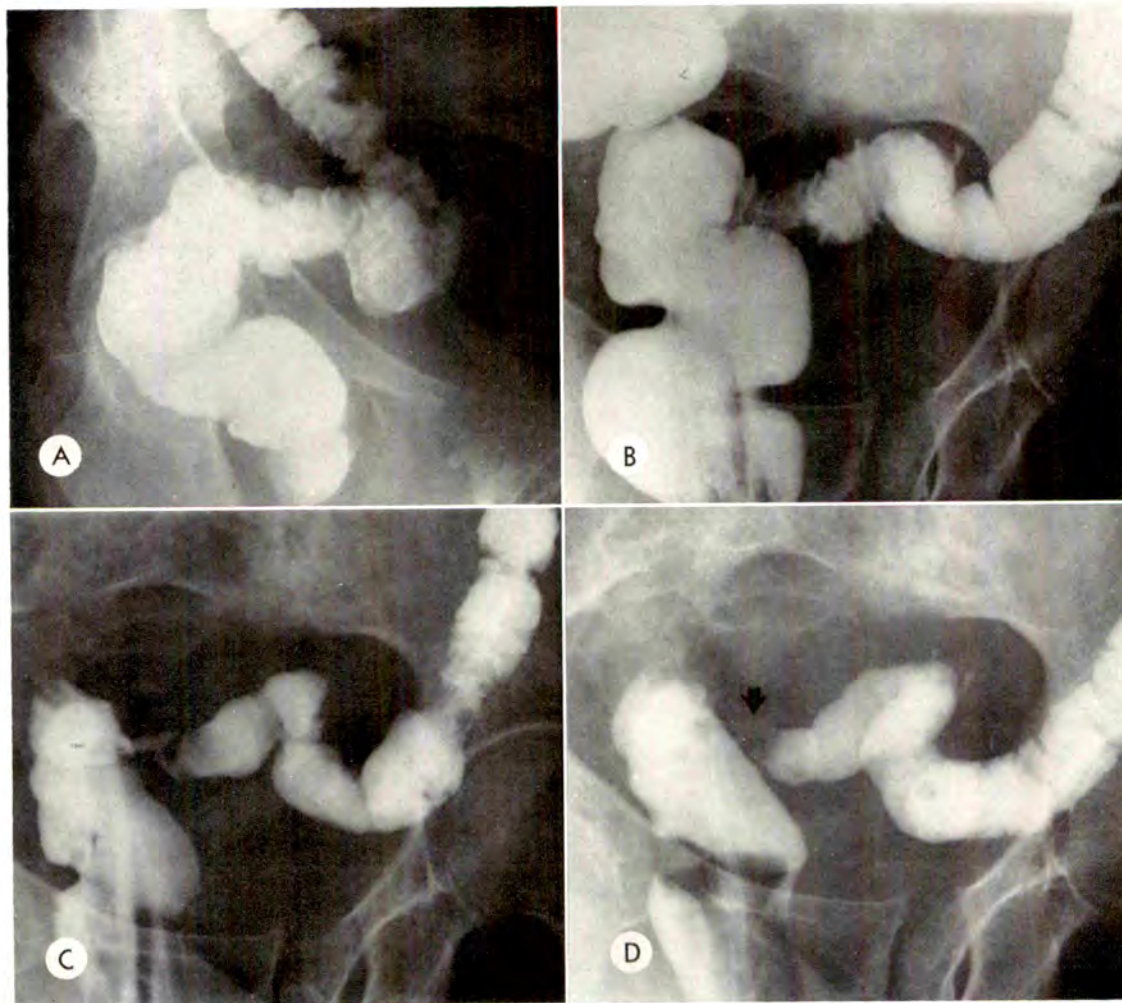


FIG. 1. *Radiation sigmoiditis*. Case S. S., Stage IIIb, treated in June, 1956, with 6,100 rads whole pelvis irradiation and 3,600 mgh of radium. Rectal bleeding developed in February, 1957 and reappeared intermittently until November, 1959. (A) The normal rectosigmoid prior to treatment. (B) February 20, 1957: the slight narrowing with intense edema of the mucosa, which is characteristic of acute radiation sigmoiditis, is evident. (C) November, 1958: marked fibrosis of the rectosigmoid has occurred without actual obstruction. (D) March, 1960: there is residual narrowing of the rectosigmoid with obliteration of the normal mucosal pattern, but there has been some re-expansion as the inflammatory process subsided and the fecal stream dilated the bowel. The patient is now four and one-half years post-treatment without evidence of disease.

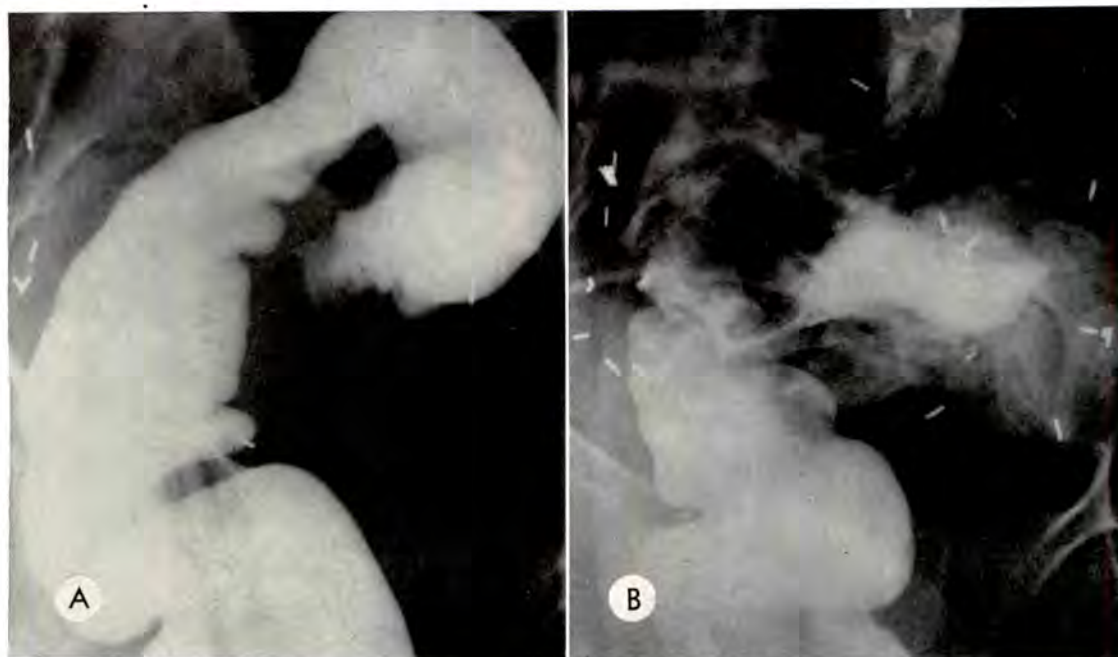


FIG. 2. Radiation sigmoiditis with perforation following local resection and primary anastomosis. Case M. W., Stage IIIA, treated in March, 1957 with 6,000 rads whole pelvis irradiation and 4,000 mgh of radium. Lymphadenectomy and left salpingo-oophorectomy for ovarian cyst were also performed. In January, 1958 the patient developed bloody stools and obstruction. (A) Although the obstruction to the retrograde flow of barium is complete, there is no significant distention of the colon proximal to the point of narrowing. Twelve inches of sigmoid were resected. In February, 1958 a pelvic abscess developed and colostomy was required. In March, 1958 a small bowel obstruction occurred and laparotomy was performed with the removal of 4 feet of ileum. The patient expired in March, 1958. (B) The breakdown of the primary anastomosis of the colon with abscess formation and cutaneous fistula is demonstrated.

fistula formations between the small bowel, vagina or pelvic cavity are seen. Despite colostomy and disuse, continuous symptoms of profuse rectal bleeding, discharge, and sepsis become prime management problems. In 2 patients, despite one resection of the sigmoid (Fig. 2, A and B) and colostomy in the other, continuing necrosis resulted in death.

Nearly 60 per cent of the cases of sigmoiditis in this study occurred within a period of six to twelve months following initial treatment. In one instance, the patient who had had previous radium treatment for a benign condition developed symptoms during therapy. In 30 per cent sigmoiditis occurred twelve to eighteen months after treatment. In 2 cases it was noted after two years. Practically all sigmoid complications can be expected to

occur within two years and only exceptionally after that time.

A few instances of sigmoiditis had been noted in the presupervoltage series. In 1954 and 1955 parametrial irradiation was still carried out with 250 kv. and some cases of sigmoiditis occurred in patients so treated (Tables VII and VIII). Three of the resections were done by a local surgeon and it is possible that there may have been some hastily performed procedures for a symptomatology which would have later subsided by itself.

There is practically no sigmoiditis in the group receiving 4,000 rads whole pelvis irradiation; without added surgical procedures, sigmoiditis will occasionally occur with 6,000 rads (Tables VII and IX). Lymphadenectomies are a contributing factor to the incidence of sigmoiditis, primarily

when done in patients receiving 6,000 rads or more whole pelvis irradiation (Table ix).

Twenty-two of the 32 cases of sigmoiditis (70 per cent) developed in patients treated in the years 1955 and 1956. Although the program of lymphadenectomies was carried out in the succeeding years, the severity and incidence of sigmoiditis had diminished. A few cases developed in patients treated in 1957 and 1958.

The surgical interventions (11 cases in the total of 32 cases of sigmoiditis of all degrees of severity) were either colostomy or local resection of a segment of the sigmoid.

The selection of colostomy or segmental resection depends on (1) the acuteness of the symptoms, (2) the extent of involvement, and (3) the degree of pelvic fibrosis and adhesions, necrosis, abscesses or fistulae. When such additional changes are present, a colostomy has to be performed. On occasion, a re-anastomosis with or without a resection of the sigmoid has been done after the acute stage has subsided.

A segmental resection undoubtedly offers the patient rapid recovery without the annoyances of a colostomy. These resections were curative and there was no recurrence of the symptoms. This is the procedure usually followed when the patients develop discomforting changes rather late (Fig. 3, *A* and *B*).

VESICO-, RECTO-, VESICORECTO-, OR URETEROVAGINAL FISTULAE

In the presupervoltage series, 12 fistulae developed, 10 in Negro patients and 2 in White patients. Fistulae in Negro patients, with 1 exception, started with vault necrosis which did not heal, whereas in the 2 White patients they originated as rectal ulcers.

In the supervoltage series, there are 12 fistulae—8 in Negro patients and 4 in White patients. Six, or 50 per cent, of the fistulae cases were in Stage III_B patients. Seven patients had had hysterectomy or exenteration and 5 had had lymphadenectomy.

TABLE VII
INCIDENCE OF SIGMOIDITIS
(September 1, 1954 to March 1, 1959)
(741 Patients)

Treatment	No. of Patients	Uncomplicated Cases		Complicated Cases		Per Cent
		No Additional Surgery	Lymphadenectomy	Fistula	Small Bowel Necroses	
Radium Only		1	0	0	0	
Radium + Parametrial Irradiation	197	3	4*	2	0	4.1
2,000 rads Whole Pelvis Irradiation + Radium	85	2	0	0	0	2.4
4,000 rads Whole Pelvis Irradiation + Radium	129	1	1	0	1	2.3
6,000 rads or More Whole Pelvis Irradiation + Radium	305	6	14	3**	5†	9.2

* 2 cases with hysterectomy and lymphadenectomy.

** With hysterectomy and lymphadenectomy.

† With Lymphadenectomy only.

(Cases noted ** and † are recorded here also for the purpose of estimating the incidence of sigmoid injuries)

TABLE VIII

BOWEL COMPLICATIONS FOLLOWING ORTHOVOLTAGE IRRADIATION AND RADIUM THERAPY

(September 1, 1954 to March 1, 1959)

(282 Patients)

Treatment	No. of Patients	Recto-, Vesico-, or Uretero-vaginal Fistula	Sigmoiditis		Sigmoiditis (surgery necessary)*	Fistula and Sigmoiditis	Small Bowel Necrosis	Small Bowel Necrosis and Fistula	Small Bowel Necrosis and Sigmoid Necrosis
			Early	Moderate					
No Added Surgery (193 Patients)									
Radium Only	138				1**				
Radium+250 kv. Parametrial Irradiation				1	2***				
2,000 rads+Radium	55		1		1				
Lymphadenectomy (68 Patients)									
Radium Only	46								
Radium+250 kv. Parametrial Irradiation					2***				
2,000 rads+Radium	22						1 ††		
Hysterectomy or Exenteration plus Lymphadenectomy (21 Patients)									
Radium Only	13								
Radium+250 kv. Parametrial Irradiation		1		1					
2,000 rads+Radium	8	1 †							

* Resection of a segment of the sigmoid or a colostomy.

** Patient had had previous radium therapy for a benign condition; colostomy was necessary.

*** Resections of the sigmoid were performed by a local medical physician; 1 case had a lymphadenectomy.

† A Stage 1 patient in whom the radium treatment was not completed because of perforation of the uterus; the patient had multiple postoperative troubles prior to the occurrence of a vesicovaginal and sigmoid vaginal fistula.

†† Patient had two separate operations, a lymphadenectomy and later a laparotomy for biopsy of a suspicious mass near the right pelvic wall; intestinal obstruction developed eight months following the last operation.

Only 2 fistulae developed in the patients treated by 2,000 rads of conventional therapy and both followed hysterectomy (Table VIII).

The fistulae were distributed as follows: rectovesicovaginal, 4 cases; vesicovaginal

(including 1 ureterovaginal), 4 cases; and rectovaginal, 4 cases.

The time of appearance of this complication varies, but it is usually within twelve months. After hysterectomy, the majority of complications appear within six to nine

months. Higher than average radiation doses in patients with advanced disease were found to be a contributory cause in many cases. In 4 cases the fistulae were found subsequent to a major surgical trauma or severe postoperative complications.

Death was attributed to the complication in 4 cases. There are 5 patients living and free from disease from three to five years.

SMALL BOWEL NECROSIS

Necrosis of the small bowel is the most severe complication of radiation treatment of cancers of the uterine cervix and has

been reported very rarely following conventional radium and parametrial roentgen irradiation. A thorough evaluation of each case has been made as the complication occurred, in order to pinpoint contributing factors.

The small bowel necroses appear approximately one year following treatment, but may occur sooner and, rarely, as late as two years after treatment. Unless symptoms from other complications are already present, they are evidenced by a sudden onset of symptoms suggestive of acute intestinal obstruction. Barium enema study is negative, indicating that the difficulty is

TABLE IX

BOWEL COMPLICATIONS FOLLOWING WHOLE PELVIS SUPERVOLTAGE IRRADIATION AND RADIUM THERAPY
(September 1, 1954 to March 1, 1959)
(434 Patients)

Treatment	No. of Patients	Recto-, Vesico-, or Uretero-vaginal Fistula	Sigmoiditis		Sigmoiditis (surgery necessary)*	Fistula and Sigmoiditis	Small Bowel Necrosis	Small Bowel Necrosis and Fistula	Small Bowel Necrosis and Sigmoid Necrosis
			Early	Moderate					
No added Surgery (231 Patients)									
4,000 rads**	73	1†		1					
6,000 rads or more***	158	1	2	3	1		1†		
Lymphadenectomy (154 Patients)									
4,000 rads**	42	1†††		1		1			
6,000 rads or more***	112	2	7	3	4		7††	1	
Hysterectomy or Exenteration plus Lymphadenectomy (49 Patients)									
4,000 rads**	14	1			1		1†††		
6,000 rads or more***	35	2				1	1†††	3†††	1†††

* Resection of a segment of the sigmoid or a colostomy.

** Total number patients 4,000 rads to whole pelvis, 129.

*** Total number patients 6,000 rads or more to whole pelvis, 305.

† Previous multiple pelvic surgical procedures in one case and in the other case laparotomy for removal of radium needle (case not suitable for intracavitary radium therapy).

†† 5 patients (all Stage IIIB, 3 having received 7,000 or 8,000 rads to the whole pelvis and 1 having had an exenteration) have died from necrosis.

††† 3 patients have died from necrosis.

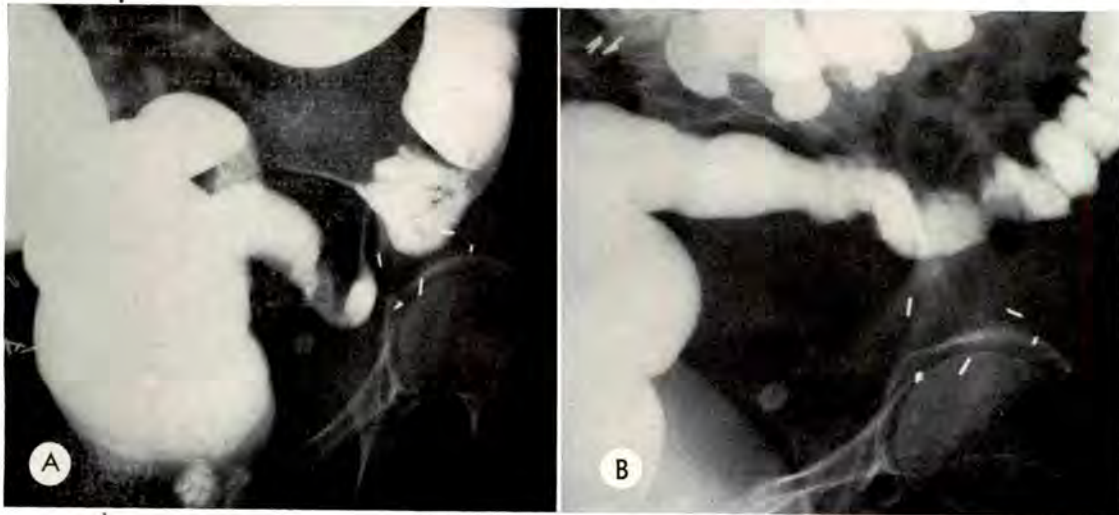


FIG. 3. *Radiation sigmoiditis with satisfactory surgical result.* Case I. C., Stage IIIA, treated in June, 1955 with 9,360 mgh of radium and 4,000 rads parametrial cobalt 60 irradiation. Lymphadenectomy and hysterectomy were performed and no carcinoma was found. (A) June, 1956: the patient developed obstruction following rectal bleeding. Resection for necrosis of the sigmoid was performed in July, 1956. (B) January, 1959: the anastomosis is shown to be functioning satisfactorily. The patient is alive and well four and one-half years after therapy. The degree of sigmoidal fibrosis was so marked in this instance that surgical resection was mandatory.

in the small bowel. An exploratory laparotomy is done following an initial attempt to relieve the obstruction by intubation, but delay in the surgical procedure may lead to perforation, thus increasing the danger of generalized peritonitis and mortality.

Even when properly managed, the prognosis for patients with this complication is discouraging. Resection of a segment of the necrotic bowel is often followed by development of a subsequent obstruction, and the chances of recovery are small.

There are minor injuries of the small bowel which are demonstrable on roentgen examination, such as ulceration of the ileal mucosa with symptoms of intermittent diarrhea, abdominal cramps and, occasionally, melena. These minor injuries usually have a favorable prognosis and subside without surgical intervention.

When small bowel necrosis is complicated by fistula, the symptoms depend upon the point of communication of the fistula, whether with the sigmoid or other loops of ileum or the vagina, or directly into the pelvic cavity forming fecal abscesses which

eventually may drain. The management of such cases is difficult and the prognosis is most grave. Usually, despite multiple surgical procedures, little can be achieved.

Tables VIII and IX show that, with 2 exceptions, the small bowel necroses occurred in the group of patients receiving 6,000 rads or more whole pelvis irradiation. There were 2 cases of small bowel necrosis which developed in the group receiving less than 6,000 rads to the whole pelvis. One patient had been treated by conventional technique, followed by lymphadenectomy and later a laparotomy was done for biopsy of a suspicious mass near the right pelvic wall. Intestinal obstruction developed subsequently. In the other case, in which small bowel obstruction developed after 4,000 rads to the whole pelvis, a hysterectomy and lymphadenectomy had been carried out.

In the group of patients having received 6,000 rads or more to the whole pelvis, the addition of lymphadenectomy or, more often, hysterectomy plus lymphadenectomy increases the risk of small bowel

necroses. The blood supply, already diminished by irradiation, is further interfered with by the surgical procedure and pressure from lymphocysts. Postoperative adhesions increase edema and precipitate the acute onset.

Sigmoiditis is often associated with small bowel injuries (Table VII; and Fig. 4, A and B).

VAULT NECROSIS

In the presupervoltage group, there were 16 temporary self-healing vault necroses in 340 White patients and 12 in 175 Negro patients, showing a somewhat greater incidence in the Negro group.

The vault necroses appeared three months to a year after the completion of treatment and were manifested by vaginal discharge with foul odor, low abdominal discomfort and pain in the suprapubic area. They healed with such conservative measures as the application of varidase or zephiran and glycerine packing with vinegar douches.

In the supervoltage series the same rela-

tive incidence of vault necroses is seen (Table x). The necroses occurred more often in the early cases, essentially because of local radium irradiation. There is no correlation with lymphadenectomies. If a hysterectomy and/or exenteration had been performed and a vault necrosis occurred, it was a complication of healing of the vault wound.

The vault necroses in the supervoltage group associated with more severe complications were more common in the Stage III_A and III_B cases than the uncomplicated ones, which indicates a more diffuse damage because of the large volume irradiated.

EXCESSIVE PELVIC FIBROSIS WITH URETERAL STRICTURES

High doses to the whole pelvis do not produce excessive pelvic fibrosis. In fact, it is our impression that the horseshoe fibrosis, except when lymphadenectomy has been performed, is less with whole pelvis irradiation using supervoltage than with the 400 kv. unit.

The cases subjected to lymphadenectomy

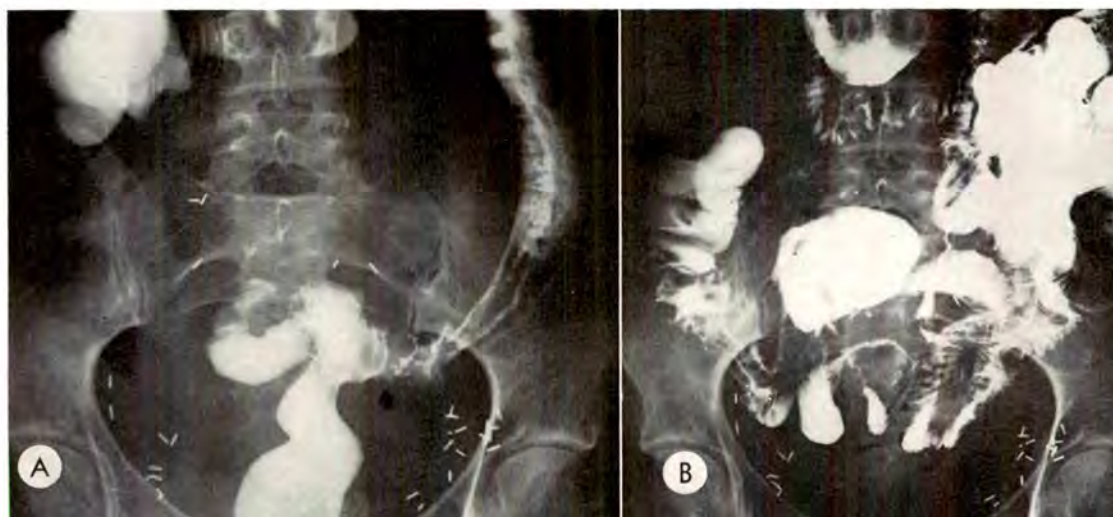


FIG. 4. *Radiation sigmoiditis and enteritis.* Case L. S., Stage III_A, treated in May, 1958 with 6,000 rads whole pelvis irradiation plus 4,400 mgh of radium. A subsequent lymphadenectomy revealed no carcinoma. (A and B) August 25 and 28, 1959: severe radiation sigmoiditis and enteritis are present. Earlier (July, 1959) a small bowel obstruction, clinically present, was spontaneously relieved. A second obstruction occurred in August, 1959; in September, 1959 ileostomy and colostomy were required. In October, 1960 the patient had been alive three years. Note the acute edema in the sigmoid region which eventually progressed to fibrosis following colostomy. Also note the large segments of small bowel involved within the treatment field, with intermittent areas of edema and fibrosis. In addition to the changes in the bowel, bilateral lymphocysts were present.

TABLE X

DISTRIBUTION OF PATIENTS WITH VAULT NECROSIS
BY STAGE OF DISEASE(September 1, 1954 to March 1, 1959)
(741 Patients)

Stage	Vault Necrosis Only	Vault Necrosis with Other Complica- tions	Total	Treatment Dose Higher Than Average
I	6	4	10	3
IIA	6	1	7	2
IIB	9	2	11	1
IIIA	7	3	10	4
IIIB	3	5	8	0
IV	1	2	3	0
All Stages	32	17	49	10

1. There is no difference in the racial distribution of patients with uncomplicated vault necrosis between the presupervoltage and supervoltage series. The incidence in the presupervoltage group was 5 per cent in White patients and 8 per cent in Negro patients; in the supervoltage group it was 4.1 per cent in White patients and 5 per cent in Negro patients.

2. In both groups 90 per cent of the vault necroses appeared within twelve months following the treatment, with 57 per cent occurring between six to twelve months. As a rule they healed spontaneously. Fifty-three per cent healed within three months and all but 2 cases healed within twelve months.

had lymphocysts of various degrees of severity and duration and this condition had produced temporary pressure on the ureters.⁶

Table XI lists the ureteral strictures by degree of severity. There are as many instances of ureteral changes at the lower dose levels as at the 6,000 rads or more dose level.

One can conclude that high dose whole pelvis irradiation (even with 6,000 rads), provided no surgical procedure is added, is not conducive to excessive fibrosis and ureteral complications.

PELVIC BONE INJURY

With the use of a four field technique including two lateral portals, the two femoral heads and necks are irradiated. The anterior and posterior portals include only a small part of the head itself and, because

of the sharp fall-off of dose, the remaining part of the head and femoral neck does not receive high doses.

There have been 3 instances of minimal changes in the femoral head. In 2, 6,500 rads had been given to the whole pelvis; in the third, treatment had been given with conventional radium and 3,000 rads to the parametria with 250 kv. followed by lymphadenectomy.

Necrosis of the femoral head developed in 1 patient two years after treatment with conventional radium and 250 kv. radiation delivered to the parametria; it required resection and a prosthesis.

A healing fracture of the ascending ramus of the pubic bone was diagnosed incidentally three years after treatment on a routine pyelogram of a patient who had

TABLE XI

URETERAL STRICTURES

(September 1, 1954 to March 1, 1959)
(741 Patients)

Degree	Treatment	Number of Patients
Mild*	Radium + Para- metrial Irradia- tion	1-Stage IIA
	2,000 rads	2-Stage I and IIA
	+ Radium	
	4,000 rads	1-Stage IIB
	6,000 rads	2-Stage IIIB (had lymphadenec- tomy)
Moderate**	2,000 rads	1-Stage IIA
	+ Radium	
	6,000 rads	1-Stage IIIB (had lymphadenec- tomy)
Severe***	4,000 rads	1-Stage IIB (had lymphadenec- tomy and hys- terectomy)†
	6,000 rads	2-Stage IIIB

* Temporary stenosis relieved later either spontaneously or following simple dilatation.

** Unilateral hydronephrosis due to stenosis.

*** Complete loss of function of one kidney as a result of ureteral stricture.

† Also recorded in small bowel necroses.

received radium and 3,000 rads to the parametria with 250 kv.

ROENTGEN DIAGNOSIS

The radiation changes in the lower gut, urinary tract and pelvic skeletal components are nonspecific and must be interpreted in terms of the previous history. In general, the presence of one complication should lead to careful investigation of all organs within the treatment fields; complaints relative to one organ may mask concomitant injury to adjacent structures. It is also of importance to recognize that the degree of damage evident roentgenographically usually is exceeded by that found at surgery or postmortem examination.

Proctitis and rectal ulcer. In the early phases of proctitis and rectal ulcer the roentgen diagnosis is dependent upon fluoroscopic and roentgenographic evidence of irritability and diminution in the caliber of the rectum. On rare occasions, a well-developed ulcer may be demonstrated, but generally the diagnosis is more reliably made by proctoscopic examination. In those instances in which the damage is severe, the end result of rectal fibrosis is roentgenologically manifested by narrowing and lack of distensibility of the rectal ampulla and/or adjacent sigmoid.

Cystitis and bladder ulcer. In the complications of cystitis and bladder ulcers no constant roentgen signs are elicitable. Occasionally, edema or spasm of the bladder will be evident by diminution of its capacity and an increase in thickness of the soft tissue shadow of the bladder wall; either may rarely be accompanied by stasis in the pelvic ureters.

Sigmoiditis. Radiation-caused sigmoiditis is the most commonly demonstrated complication. It may vary in degree from slight edema of the mucosa to complete obstruction of the bowel lumen. In the acute stage, irritability, palpable tenderness of the segment and a decrease in the caliber of the lumen is noted fluoroscopically. Spot roentgenograms demonstrate

intact but edematous mucosa. In the more severe cases complete obstruction to the retrograde flow of barium may occur, but this is not necessarily coupled with distention of the proximal bowel. Recovery may be complete without surgical intervention. If fibrosis occurs, surgical resection may be required or eventually the segment of involved bowel may dilate sufficiently in response to the fecal stream to produce a relatively normal channel. Fistulae with adjacent organs are commonplace (Fig. 5), but occasionally small tracts are present which may not be immediately evident. It is recommended that four to six hour post-evacuation roentgenograms be taken, since fistulae not otherwise detectable may thus be demonstrated.

The basic process is essentially one of acute inflammation which must be differentiated from diverticulitis and segmental colitis of other origin.

Fistula. Fistulae between the rectum, bladder, vagina, and adjacent small intestine or lymphocysts all have been demonstrated in this series. Such involvement may affect two or more structures. The fistulae

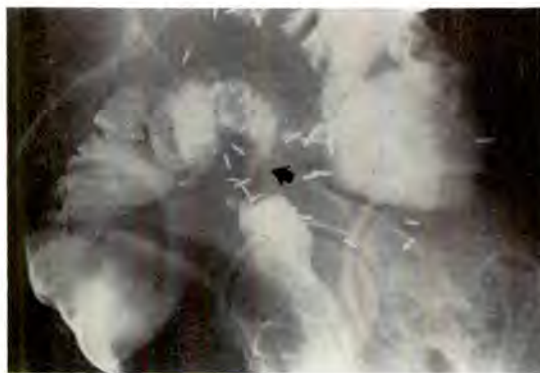


FIG. 5. Radiation Sigmoiditis with vaginal fistula. Case G. H., Stage II_B, treated with the cobalt 60 unit in August, 1955 with 4,000 rads whole pelvis irradiation plus 5,000 rads to the pelvic walls, and 6,240 mgh of radium. Subsequent pelvic lymphadenectomy disclosed no carcinoma, but marked reaction at the sigmoid was noted. In April, 1956, a sigmoidovaginal fistula developed. Amazingly, the patient was asymptomatic and in August, 1956, succumbed to a heart attack while working.

may be evident clinically when not demonstrable roentgenographically. A fistulous tract which may fill from one orifice will not necessarily fill from the other and, as previously noted, follow-up roentgenograms are of value in demonstrating the smaller communication.

Small bowel necrosis. The roentgen changes in small bowel necrosis are essentially those of any inflammatory process. In the early stages intense edema of the mucosa with interspaced areas of narrowing or bizarre configurations of the lumen are seen in long segments of the bowel. In the later stages, fibrotic areas are identifiable. Multiple fistulae between adjacent loops or other organs may develop. Not uncommonly, partial or complete intestinal obstruction will be present. Invariably the extent of the damage exceeds that demonstrated roentgenographically. Commonly, attempts at resection and anastomosis fail because of unrecognized devitalization.

The diagnosis is best made by a small bowel study employing barium sulphate. However, in instances with complete or partial obstruction the water soluble contrast media are preferable.

Vault necrosis. Vault necrosis is essentially a clinical complication which is demonstrable roentgenographically only when a fistula develops.

Excessive pelvic fibrosis with ureteral stricture. From a roentgenographic standpoint, the diagnosis of excessive pelvic fibrosis with ureteral stricture must be made by exclusion. When a retrograde or intravenous pyelogram demonstrates a smooth conical obstruction of the pelvic ureter, the diagnosis must be determined differentially between obstruction by post-operative pelvic lymphocysts, recurrent tumor, or ureteral fibrosis. If all other potential causes can be excluded, the diagnosis of ureteral fibrosis should be considered and dilatation attempted. The essential roentgen finding is one of nonspecific ureteral obstruction (Fig. 6).

Pelvic bone injury. Radionecrosis of bone is an uncommon sequela of supervoltage



FIG. 6. *Postirradiation fibrosis of the ureter.* Case E. A., Stage IIA, treated in January, 1956 with 2,000 rads whole pelvis irradiation and 3,300 rads parametrial irradiation plus 8,520 mgh radium. In June, 1958 a right hydronephrosis developed. Note that, although the point of maximum narrowing is in the region of the ureterovesical junction, the right ureter is narrowed throughout its pelvic course. The ureter was dilated and the patient is living and well four and one-half years after treatment.

treatment. The condition is essentially one of aseptic necrosis and the roentgen appearances are identical with those aseptic necroses caused by other factors (Fig. 7). The basic histologic picture is one of obliteration and sclerosis of the blood vessels coupled with absorption of bone and increase in the size and fat content of the marrow spaces. Lack of new bone formation is also a feature. Fractures are the usual pelvic manifestation of radiation damage and in the initial healing stage there is little to distinguish them from fractures of advancing age. However, resorption about the fracture margins eventually occurs with

failure of new bone formation. In addition to the osteoclastic changes described, sclerotic changes have been noted in the wings of the sacrum in a series of patients who have received supervoltage therapy (Fig. 8). These sclerotic changes may develop several years after treatment and consist essentially of marked thickening of the individual sacral trabeculae. The changes parallel the fields of treatment, but no



FIG. 7. *Radiation necrosis of the right femoral head.* Case C. K., Stage IIB, treated with 6,500 rads whole pelvis irradiation and radium. Subsequent lymphadenectomy yielded negative lymph nodes. Hysterectomy was performed for recurrence in the cervix. On December 28, 1960 marked narrowing of the right femoropelvic articulation was demonstrated coupled with early fragmentation of the femoral articular surface. The joint and opposing surface had been normal prior to therapy. In addition the patient developed a right lymphocyst and radiation rectosigmoiditis and ileitis. A fistula eventually formed between the cecum, the right lymphocyst, the vagina, the sigmoid and bladder. The patient died of inanition two years after treatment without evidence of tumor.



FIG. 8. *Radiation injury of bone.* Case F. M., Stage I, treated in February, 1955 with 8,700 mgh of radium and 3,000 rads of parametrial irradiation delivered by the 250 kv. unit. In April, 1956 the patient developed rectal bleeding but had a negative barium enema study. Rectal bleeding recurred in August, 1956, then in May, 1960 a bowel resection for sigmoiditis was performed elsewhere. In January, 1958 at this institution a radiation fracture at the junction of the right ischium and pubis was demonstrated (arrow) as well as moderate sclerosis of the sacrum, a finding apparently attributable to irradiation. As of June, 1960 the patient was alive and well five years after treatment, without evidence of disease.

determination of the underlying mechanism has been made as of this date.

DISCUSSION

The relative incidence of the classic complications in our presupervoltage and supervoltage series are tabulated in Table XII. The presupervoltage series are subdivided into two groups, the division occurring with the initiation of elaborate dosimetric procedures in 1952, which resulted in a significant diminution in some of the complications.¹

It can be seen that the incidence of minor rectal or bladder complications or fistulae is similar in both the presupervoltage and supervoltage groups with the exception of the lasting dysurias, which seem to be slightly more common in the supervoltage series. However, the same criteria of severity may not have been applied in the two series. Surgical procedures may be a contributing factor.

fistulae occurred in 21.5 per cent (24 of 112 patients) of the patients with lymphadenectomy and also in about 23 per cent (8 of 35 patients) of the group which had hysterectomy or exenteration with lymphadenectomy. Without any obvious change in the irradiation or surgical techniques, the complications in the patients who had surgical procedures were less in the years 1957, 1958, and 1959.

Irradiation with 7,000 and 8,000 rads is justified in the advanced cases as the incidence of severe complications is low.

In patients having recurrent disease, hysterectomy or exenteration can be considered if there is a possibility of control of the disease. Eight thousand rads given to the whole pelvis in eight to nine weeks may be regarded as the maximum safe radical therapy. Since a number of patients were lost because of complications, the benefits derived from radical therapy techniques in the advanced cases are overshadowed.

CONCLUSION

Various types and degrees of severity of complications in the bladder, bowels, bones, and ureters have been correlated with conventional techniques of radium and external irradiation in the early cases of squamous cell carcinoma of the uterine cervix and two major steps of whole pelvis high dose irradiation with 4,000 and 6,000 rads or more in the advanced cases.

Concomitant with this experimental radiotherapeutic program, lymphadenectomy was carried out systematically and an attempt was made to eradicate residual or recurrent disease by radical surgery.

If one delivers 4,000 rads to the whole pelvis, followed with approximately 5,500 to 6,500 mgh of radium, there is a low incidence of any type of complication and

radical surgical procedures can be performed safely.

Six thousand rads whole pelvis irradiation and, occasionally, for the very advanced cases, 7,000 or 8,000 rads can also be used, but surgical procedures can be contemplated only if there is evident residual or recurrent cancer. Additional elective procedures are not justified as the incidence of severe complications amounts to approximately 20 per cent in patients submitted to radical irradiation and radical surgery.

As expected, there are no skin complications of even minor degree.

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PYELOGRAPHIC ANALYSIS OF RADIATION THERAPY IN CARCINOMA OF THE CERVIX*

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FROM January 1, 1948 through December 31, 1959, excretory urograms were obtained in 305 patients with carcinoma of the cervix prior to the initiation of radiation therapy. Of these patients, 43 were found to have abnormal pyelograms secondary to obstruction. In these patients, the obstruction must be assumed to have been caused by extension of the cervical neoplasm. Of the entire group of patients, 14.1 per cent had abnormal pretreatment pyelograms as opposed to 1.4 per cent with unilateral and 0.6 per cent with bilateral involvement in a noncarcinomatous group studied at autopsy.¹¹

INCIDENCE AND SIGNIFICANCE OF ABNORMAL PYELOGRAPHIC FINDINGS

The incidence of the abnormal pretreatment pyelograms is listed in Table I. These figures are somewhat lower than reported by several other series,^{1,7} but closely correlate with those of Pomeroy.¹⁵

The frequency of abnormal pyelographic findings is as one would expect, since the predilection of carcinoma of the cervix to involve the ureters and bladder is well known clinically. These figures reflect the pathogenesis of this neoplasm. Table II shows the distribution of the obstruction in the 43 patients. The neoplasm shows no predilection for one side over the other, but tends to spread diffusely along the base of the bladder and lower ureter by both direct infiltration and lymphatic extension.

The prognostic significance of patients who received radiation therapy for cervical carcinoma with abnormal pretreatment pyelograms and those with normal pretreatment studies is revealed by the statistics in Table III. Of those patients with

TABLE I
ABNORMAL PYELOGRAMS

Stage	No. of Patients	No. with Abnormal Pyelograms	Per Cent with Abnormal Pyelograms
I	73	3	4.1
II	122	8	6.6
III	78	13	16.7
IV	32	19	59.4
Total	305	43	14.1

abnormal pretreatment pyelograms, only 40 per cent lived one year following treatment as compared to 80.6 per cent of those with normal pretreatment pyelograms. Within each stage of carcinoma of the uterine cervix, the abnormal findings on pretreatment pyelograms diminish the chance of the patient surviving one year by approximately 50 per cent.

Despite the high incidence of death secondary to renal failure in patients with carcinoma of the cervix reported by many authors,^{2,3,8,10,18} no deaths from renal failure occurred during treatment in our 43 patients showing ureteral obstruction on pretreatment pyelograms.

The therapy employed in these patients was that of a modified Manchester technique: two standard radium applications and external irradiation with delivery of approximately 7,000–10,000 r to Point A, and 5,000–6,000 r to Point B. Despite this dosage of radiation, only one patient demonstrated permanent improvement on the pyelogram following treatment. This patient had a Stage III tumor with a Grade III hydronephrosis on the right prior to radiation therapy. Twelve months following

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TABLE II
DISTRIBUTION OF OBSTRUCTION

Stage	Right	Left	Bilateral
I	2	0	1
II	3	4	1
III	4	8	1
IV	6	7	6
Total	15	19	9

therapy, the pyelograms were normal bilaterally and eight years later the patient was alive and well. One wonders if the obstructions were not the result of parametritis so often present⁶ and not the malignancy. Three additional patients demonstrated a temporary decrease in the degree of obstruction two to fourteen months following radiation therapy but eventually succumbed to their disease.

Fifty-two patients demonstrated roentgenographic evidence of ureteral obstruction following therapy and of these 49 or 94.2 per cent ultimately proved to have persistent neoplasm in the pelvis or distant metastasis. Three patients (who received treatment here) were found to have obstruction, but no demonstrable neoplasm. At surgical exploration these patients were found to have ureteral stricture secondary to radiation fibrosis.

The average time of onset of the fibrosis following radiation therapy in our patients was thirty-seven months, ranging from twenty-eight to fifty-two months. Contrasted with this is the group which developed obstruction following therapy and

in which tumor was found (Table IV). These patients showed obstructive changes an average of 12.2 months after therapy with a range of 0-48 months. Radiation strictures of the ureter appeared much later than recurrent tumor.

The incidence of ureteral stricture secondary to irradiation is unknown, but in our series it represents about 1 per cent of all patients treated for carcinoma of the cervix and 5.8 per cent of those patients showing abnormal pyelograms following treatment. This compares closely with Sörénson's¹⁶ findings in a controlled population in Sweden. Since these patients have not been aggressively searched for, the figures are minimal.

We perform pretreatment and posttreatment pyelography routinely. When evidence of obstruction is demonstrated, a pelvic examination and biopsies from the cervix and parametrial tissues are done. A roentgenogram of the chest is made and cystoscopy, as well as sigmoidoscopy and a barium enema examination are performed. If no tumor is found, then exploratory laparotomy is carried out.

The lesion is one of fibrosis, most commonly 4-6 cm. from the ureteral orifice at a point where the ureter traverses the broad ligament,^{4,5,9,12,17} although, in one case the lesion was 15 cm. from the ureteral orifice in the region of the pelvic brim. Whether the lesion is the direct result of radiation injury to the ureteral wall, fibrosis secondary to the associated parametritis, replacement of necrotic tumor by fibrous tissue or a combination of factors is un-

TABLE III
STATISTICS SHOWING PROGNOSTIC SIGNIFICANCE

Stage	Normal Intravenous Pyelograms		Per Cent	Abnormal Intravenous Pyelograms		Per Cent
	No.	No. Alive 1 Yr.		No.	No. Alive 1 Yr.	
II	105	91	86.6	8	5	55.5
III	65	49	75.4	13	5	38.5
IV	11	6	54.5	19	6	31.6
Total	181	146	80.6	40	16	40

TABLE IV

UPPER URINARY TRACT OBSTRUCTION DEVELOPING
AFTER RADIATION THERAPY FOR CARCINOMA
OF THE CERVIX

Stage	No. of Patients	Range (mo.)	Average (mo.)
I	14	0-43	21.0
II	34	2-48	16.9
III	24	0-48	11.6
			Av. 12.2
IV	1	3 months after therapy	

known. The patients in our series, however, were free of tumor and cured of their disease.

TREATMENT

Three types of therapy have been suggested. We feel that nephrectomy should not be performed since conservation of renal tissue is of paramount importance. Nephrostomy temporizes, but does not restore continuity of the urinary tract. Some authors have advocated the use of ureteral dilatations of the stenotic area.^{9,13} Our experience is similar to that of Valk,¹⁷ who states that in no cases was he able to cause regression of the hydronephrosis. In all of our cases, the continuity of the urinary system was maintained by uretero-neocystostomy,¹⁴ with relief of the obstruction and preservation of the renal tissue.

CONCLUSION

In the light of our findings, it seems apparent that radiation therapy alone is inadequate for treating those patients with carcinoma of the cervix who show abnormal pretreatment pyelograms. The question of increasing the dosage has been raised but this seems hazardous unless new techniques are developed. The role of surgery and radiation combinations is now being re-evaluated.

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THE USE OF A DIAMOND SHAPED FIELD IN IRRADIATION OF PELVIC ORGANS, PARTICULARLY IN CARCINOMA OF THE CERVIX UTERI*

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IN HIS paper presented at the Annual Meeting of the American Radium Society in 1956, Twombly⁴ demonstrated the location of the most frequently involved lymph nodes, in cancer of the cervix, in relation to the bony pelvis and external body landmarks, such as the inguinal folds and the umbilicus. These are shown in Figure 1 reproduced with his permission, where the position of the obturator lymph nodes, high in the pelvis above the acetabulum, should be especially noted. Conditions in individual patients will vary considerably depending on the extent of the disease and the anatomic variations in the form and tilt of the pelvis. Dr. Twombly's contention that radiotherapists routinely position pelvic fields too low would appear to be justified.

The increased use of supervoltage equipment for irradiation of the pelvis has made multiple port therapy less common and has established the 15×15 cm. opposing frontal fields as the most suitable radiation ports. External irradiation is given through either an open field or, when in combination with intracavitary radium application, through a field divider designed so as to cast a shadow 5 cm. wide at the level of the uterus and extending 10 cm. cephalad from the lower margin of the field. This shielded area covers the vagina and the lower uterine segment which have been heavily irradiated by the intravaginal and intrauterine radium. The resulting field has the shape of an inverted U.

In those patients who have not received intracavitary radium, the upper half of the vagina should be included in the treatment field. To accomplish this, inguinal areas as



FIG. 1. Location of various structures in the pelvis. The diagonal lead wires lie in the groins over Poupart's ligaments. The vertical wire is in the uterine canal, its lower end exactly at the external os. The circle surrounds the umbilicus. The silver clip to the right of it lies just below the bifurcation of the aorta. The single clips over each sacroiliac joint are in the bifurcations of the common iliac arteries. The clips on the patient's right, in the shape of a cross, lie in the center of the obturator fossa at the location of the "obturator lymph nodes." (Reproduced with permission.⁴)

well as the acetabulum, medial portions of the femoral heads, and segments of the inner aspect of the thighs are irradiated. In addition, segments of intestine and sometimes even the lower poles of the kidneys are included in the upper corners of such a field. In cases where there is evidence of upward extension of the cancer, enlarging the field increases the irradiated volume and limits the total dose. The application of a circular field results in a considerable reduction of the irradiated volume, but the

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majority of supervoltage machines are equipped with collimators that give only rectangular fields. Field shaping devices could be used, but these are usually cumbersome, heavy and difficult to apply.

DIAMOND SHAPED FIELD

It was observed that if the conventionally positioned treatment field was rotated 45° about the beam axis, a 35 per cent reduction in field size (from 15×15 cm. to 12×12 cm.) could be achieved without omission of any critical sites from the treatment field and with a considerable reduction in dose to outlying, uninvolved structures.

As a result of the reduction in field size, there is a corresponding reduction in integral dose. Although the transverse diameter of a 12×12 cm. field is 17 cm., the effective length and width of a diamond shaped field is not appreciably different from those of the conventionally placed 15×15 cm. field because of the more rapid fall-off of intensity at the corners of the field as compared to the sides. Figure 2, *A* and *B* shows the external placement of the diamond shaped field and an alignment radio-

graph made with the AECL Eldorado cobalt 60 teletherapy unit.

DOSE DISTRIBUTION

In order to assure that a sufficient dose is delivered to all regions enclosed by the treatment field, as shown by the alignment radiograph, the dose distribution was measured in a plane perpendicular to the axis of the beam and at a depth of 10 cm. within a presswood phantom. The field size on the surface of the phantom, as indicated by the light beam, is 12×12 cm. at 80 cm. skin source distance. At 10 cm. depth, the geometric edge of the beam is 13.5×13.5 cm. The field divider consists of a lead block 3.5 cm. wide and 5 cm. thick. This is supported upon a lucite tray 70 cm. from the source. The field size, as defined by the light beam localizer of the AECL Eldorado unit, corresponds to the 20 per cent isodose curve of the gamma-ray beam.

An automatic field mapping device² utilizing an anthracene crystal detector 5 mm. in diameter measured the dose distributions with and without a cervical-vaginal shield. These are shown in Figure 3,

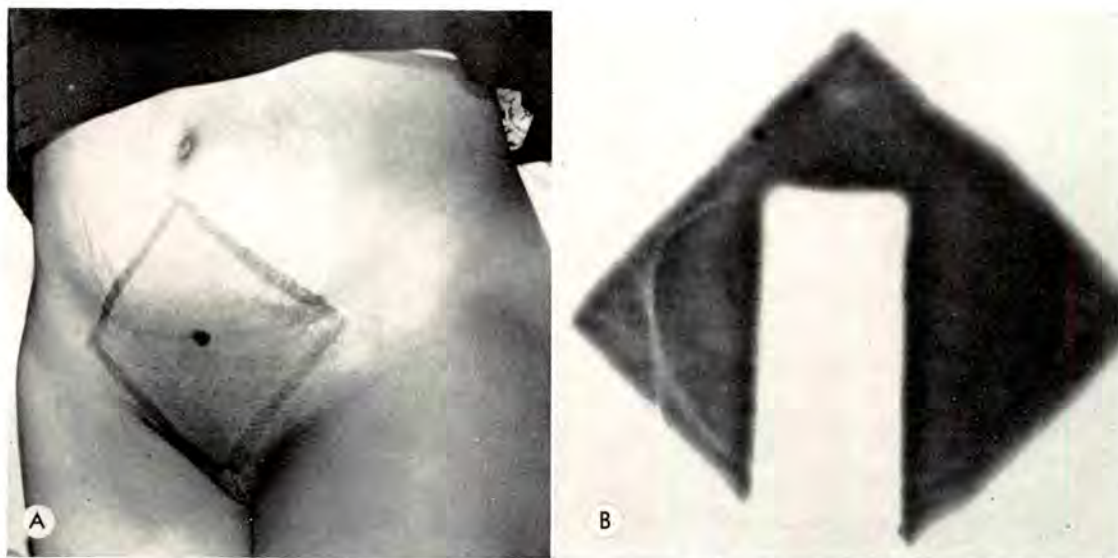


FIG. 2. (*A*) External placement of the diamond shaped field and (*B*) localization radiograph made under treatment conditions. The field divider was placed to correspond with the position of the radium tandem in the uterus.

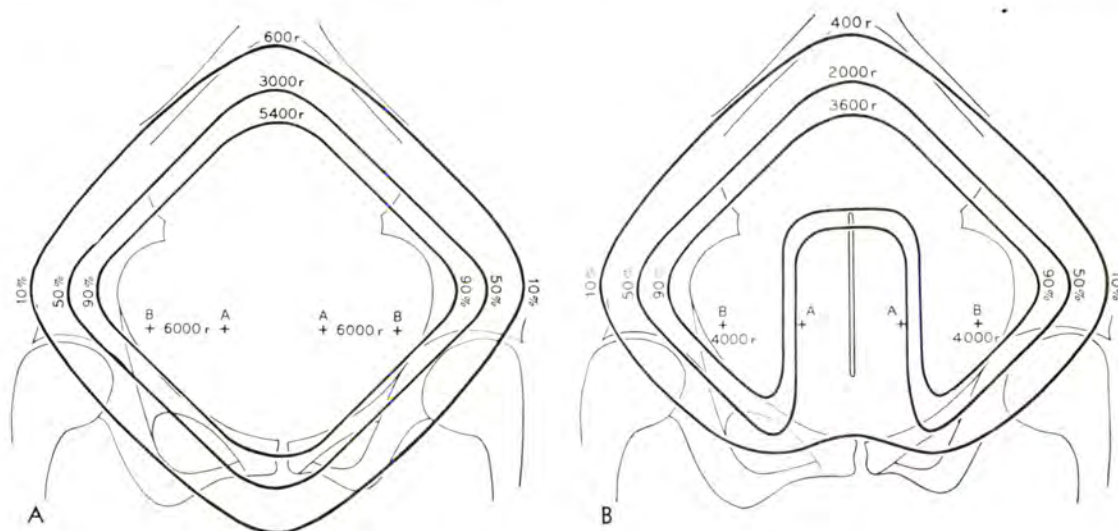


FIG. 3. Dose distributions at a depth of 10 cm. for a 12×12 cm. field at 80 cm. skin source distance. (A) The distribution with a dose of 6,000 r to point B. (B) The distribution with a cervical-vaginal shield and a dose of 4,000 r to point B.

A and B superimposed upon those portions of the anatomy enclosed by these fields. The isodose curves are related to doses to point B of 6,000 r for the full diamond shaped field and 4,000 r for the diamond shaped field modified by the dividing lead shield. By way of comparison, the dose distribution at a depth of 10 cm. for the

conventional 15×15 cm. field is shown in Figure 4.

Of primary importance is the dose distribution which results from combined radium and telecobalt therapy. Following the procedure outlined by Silverstone, Harris and Greenberg,³ doses of 6,400 r to point A and 2,000 r to point B are delivered

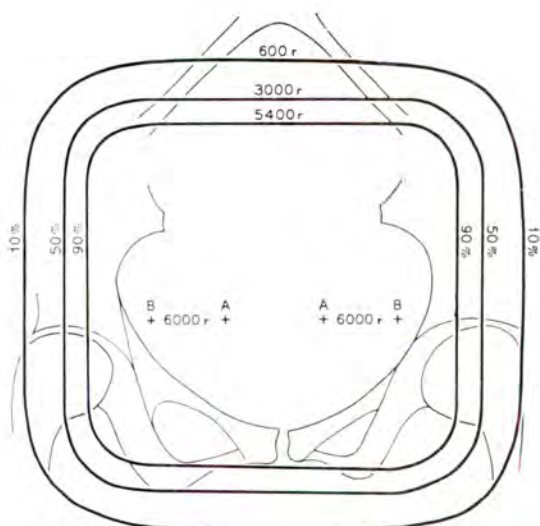


FIG. 4. The dose distribution for the conventionally placed 15×15 cm. field for a dose of 6,000 r to point B.

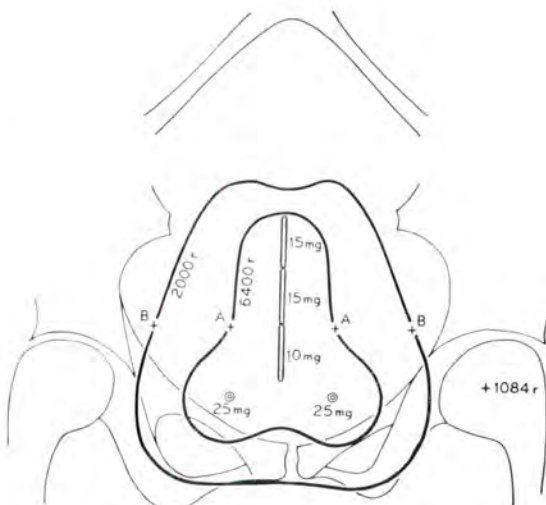


FIG. 5. The dose distribution when point A receives 4,000 r from the tandem and 2,400 r from the colpostat.

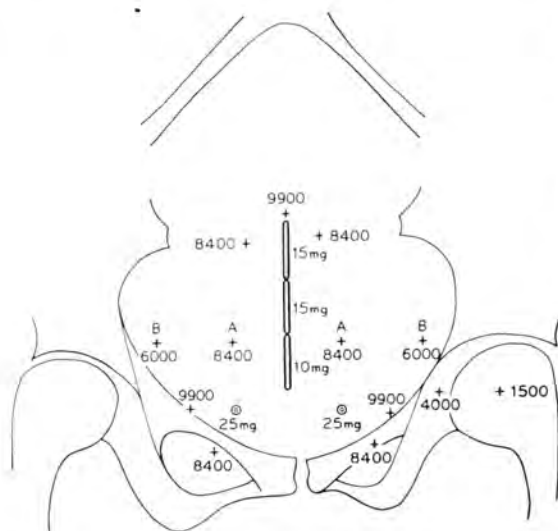


FIG. 6. Doses delivered to various points by the combined radium system and telecobalt therapy, using the split diamond shaped field.

by a radium applicator consisting of a tandem loaded with 10-15-15 mg. and a colpostat containing two 25 mg. tubes. These are inserted separately with a two to three day interval between the first and second insertions. The dose distribution obtained from the radium application is shown in Figure 5. Doses to several points in the vicinity of the uterus which result from the combination of radium and the split diamond shaped field are shown in Figure 6. Friedell and Parsons¹ have reported that uterine cancer almost always spreads to the paracervical and paravaginal tissues. As regards these regions, the dose distribution using the diamond shaped field is essentially

the same as that obtained with the conventional field.

SUMMARY

The use of a diamond shaped field for pelvic irradiation results in essentially the same dose distribution within the pelvis as that obtained with conventionally positioned rectangular fields. Because the border of the diamond shaped field aligns very closely with the inner surface of the pelvis, the conventional 15×15 cm. field can be reduced to a 12×12 cm. diamond shaped field. The advantages to be gained are a 35 per cent reduction in integral dose and the omission of uninvolved structures from the treatment field.

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CAN RADIOSENSITIVITY AND HISTOPATHOLOGY OF CERVICAL CANCER BE CORRELATED?*

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CARCINOMA of the cervix uteri in the United States is most usually treated with radiation therapy. The distribution of the forms of treatment in the patients reported to the Tumor Registry operated by the Connecticut State Department of Health are given in Table I.⁶ These indicate that in recent years 66.4 per cent have been treated by radiation alone, 11.9 per cent by radiation plus surgery and 16.7 per cent by surgery alone.

Among patients treated radiologically at Memorial Hospital, New York²⁹ in the period 1934-1941 inclusive, there did not seem to be any consistent improvement in the results of the management of carcinoma of the cervix during these years. Furthermore, Munnell and Brunschwig²⁹ state that a perusal of reports from widely scattered centers elsewhere in the country leads to a similar impression. From this it seems that the question should be raised whether the exclusive treatment of cancer of the cervix

by radiotherapeutic methods should be continued or whether this should be combined with some other form of therapy, or in some instances be completely replaced by surgical therapy. In the earlier years of this century, radical hysterectomy was accompanied by a very high mortality rate and this discouraged surgical attempts in the field. The results obtained by Meigs,²⁶ however, indicate that modern surgical techniques do not result in significant mortality of themselves. The problem then is to decide which cases should be treated radiologically and which surgically. "The possibility remains that surgery and radiation might best serve the patient as complementary rather than competitive forms of treatment."⁷

The concept of radiosensitive and radio-resistant cancer has developed. Kottmeier²³ doubts the existence of a radioresistant cancer in the cervix and rather than basing response on radiosensitivity he bases it on varying degrees of malignancy of varying cancers. Although Glucksmann and Way¹³ have not come to this conclusion from their study, Kottmeier²³ believes that their studies agree with his opinion. Warren³³ states that radiosensitivity is relative and he divides radiation response into: *radio-sensitive* tumors which regress strikingly or disappear with 2,500 r or less but without damage to the normal tissue; *radioresponsive* with regression following 2,500 to 5,000 r and with the normal tissue showing definite reaction but usually recovering after cessation of therapy; and *radioresistant* in which more than 5,000 r is necessary for response and damage to the normal tissue may equal or exceed that of the

TABLE I

PERCENTAGE DISTRIBUTION BY TREATMENT DURING THE FIRST COURSE OF THERAPY REPORTED BY THE TUMOR REGISTRY⁶

Type of Treatment	All Stages	
	1935-1944	1945-1954
Total No. of Cases	1,628	2,094
Percentage Distribution		
Total	100.0	100.0
Surgery	6.8	16.7
Radiation	78.2	66.4
Surgery plus Radiation	8.3	11.9
Other Treatment	0.7	0.1
No Treatment	6.0	4.9

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Part of Panel Discussion: Radiosensitivity and radiocurability as judged by microscopic techniques.

tumor. He considers that in general cervical carcinoma falls into the radioresponsive group. It must at this point be stressed that radiosensitivity and radiocurability are not synonymous. Furthermore, radiosensitivity is not a permanent unchanging feature. As a result, on a variation in radiosensitivity in the same tumor at various times or in the same tumor at different sites have been based some of the postulated factors important in radiation response in tumors.

Healing of the primary lesion after irradiation is considered to indicate radiosensitivity.¹⁶ Failure of the lesion to diminish in size may be taken as poor response to radiation or as radioresistance. On the other hand, shrinkage of the tumor, its apparent disappearance or its replacement by necrotic material would all be suggestive of radiosensitivity, but not necessarily be so. For this reason microscopic examination of the tissue is important. The area suggested for biopsy is the growing edge of the tumor. This may be difficult to find and indeed some consider that any form of serial biopsy of the cervix is contraindicated since this may interfere with healing.

Radiocurability while presumably in some way related to radiosensitivity is a different matter, and it does not follow that a radiosensitive tumor will necessarily be radiocurable! This may be determined only after a given period of time, usually five years, sometimes^{20,21} without evidence of tumor. Even under these circumstances

absolute radiocurability is difficult to establish. The inadequacy of a five year survival rate as an index of cure was illustrated by Cutler and associates,⁶ who found that the relative survival rate from the fifth to the fifteenth year was only 76 per cent of the expected rate.

It is fairly generally agreed that no prognostication may be made from an initial biopsy as to whether the tumor will be radiosensitive or radioresistant. It has been postulated that well differentiated tumors respond less satisfactorily to radiation therapy. This is not generally accepted and most authors^{1,21} were unable to correlate histologic grade with survival. On the other hand Warren and associates²⁴ tended to link results to some extent with the histologic grade. From their figures there is suggestive evidence that patients with Grade II squamous cell carcinoma have a somewhat better prognosis than those with Grade III squamous cell carcinoma. In both of these groups, however, the figures are extremely small and probably not statistically significant. Novak³⁰ observed that 10 of 12 cases considered to be definitely radioresistant were well differentiated.

On the other hand in the group reported by Glucksmann,¹¹ the correlation between tumor type and cure rate suggests that histologic grading before treatment may have prognostic significance (Table II). The tumors are classified as differentiated (D) and anaplastic (A) squamous cell

TABLE II
HISTOLOGIC TYPE OF CERVICAL CARCINOMAS AND "CURE" BY RADIUM TREATMENT
REPORTED BY GLUCKSMANN¹¹

Stage	D Differentiated		A Anaplastic		C Adenocarcinoma		M Mixed	
	No. of Cases	Per Cent Cured	No. of Cases	Per Cent Cured	No. of Cases	Per Cent Cured	No. of Cases	Per Cent Cured
I-IV	130	49	485	17	22	9	72	3
I	57	79	102	33	5	(40)	19	5
II	57	28	232	19	14	0	32	3
I and II	114	53	334	23	19	10	51	4

carcinomas, adenocarcinomas (C) and mixed carcinomas containing both columnar and squamous strains. Since he considers that the anaplastic tumors are more likely to have spread, this may be correlated with clinical stage rather than purely histologic grade.

Interesting studies have been made with tissue cultures of single mammalian cells. Puck and Marcus,³¹ using a preparation in which were suspended single He La cells derived from human cervical carcinoma, by a plating technique were able to develop 100 per cent growth of microscopic colonies in control specimens without irradiation. They found that irradiation killed the cells with the extent of damage depending on the dose. With irradiation there were fewer colonies and these colonies were smaller than those usually formed. The problems of assessment were complicated by slow growing survivors and some cells which, although lethally damaged, may multiply five or six generations and then terminate their reproduction. It was necessary, therefore, to distinguish between abortive colonies which were usually distinguished by a preponderance of giant cells and the slow growing survivors. Inactivated cells occasionally underwent the limited division forming microcolonies, sometimes remained as single cells often with the development of a giant cell and sometimes disappeared. The giant cells are interesting in that they metabolize at a higher rate, change the pH of a standard growth medium at a rate roughly comparable to that of an equal mass of actively dividing cells and could be maintained metabolically active for long periods of time if the medium were regularly replaced. Nevertheless, they had lost their ability to multiply. With higher doses there was damage to the reproductive apparatus and it was considered that the lethal effect was mostly in the genetic apparatus, a radiation induced genetic effect which was probably not a simple single gene inactivation and in which the locus of action could be chromosomal. With very high doses the cells disappeared and

the yield of giant cells dropped. The possibility of deciding by tissue culture between radiosensitive and radioresistant cervical carcinomas for choice of therapy has been investigated by Miller and associates²⁷ but this has been more or less on an experimental basis.

It has been observed that when an experienced examiner suggests that there has been recurrent carcinoma of the cervix following irradiation, the chance is 88 per cent that his suspicion is correct.³ This would indicate the value of careful gross clinical observation.

Methods of determining radiation response in tumor cells in biopsies vary considerably. In most studies a biopsy is taken before treatment as a standard. Then subsequent biopsies are taken after roentgen therapy, after first radium application, after second radium application and three months later. Warren and associates³⁴ considered that moderate radiation reaction is characterized by diminution of mitotic activity, some necrosis and vacuolization of cytoplasm, but that the tumor is still recognizable. With marked radiation reaction, mitoses are rare or absent. There is much necrosis and practically all the cells are abnormal, either vacuolated or markedly distorted or swollen with large hyperchromatic nuclei. There are only scattered tumor cells or small clusters. They based necrosis of tumor cells on acidophilic cytoplasm with indefiniteness of staining, pyknosis of nuclei or nuclear material, karyorrhexis, invasion by polymorphonuclear leukocytes and loss of cell membranes. These are, in general, the evidences of radiation reaction that are commonly accepted.

Warren and associates³⁴ also draw attention to the important stromal changes occurring in response to irradiation. Moderate radiation reaction is characterized by mild telangiectasis or thrombosis, slight fibrosis, mild hyalinization of collagen and later slight thickening of arteriolar and venule walls with hyalin deposition. Marked radiation reaction is characterized

TABLE III

COMPARISON OF CELL POPULATION OF STRATIFIED SQUAMOUS EPITHELIUM AND EPIDERMOID CARCINOMA REPORTED BY MITRA AND DE²⁸

	No. of Cases	Resting Phase	Mitotic Phase	Differentiated Phase	Degenerating Phase
Stratified squamous epithelium	56	48.76	0.75	48.17	2.30
Epidermoid carcinoma	439	84.16	4.68	3.57	7.59

by marked thickening of vessel walls with hyalin deposition or actual necrosis of the walls with thrombosis, an appreciable increase in fibrosis and marked hyalinization of collagen sometimes with foci of necrosis.

The importance of the tumor bed has been emphasized by Jolles and Koller,¹⁹ who drew attention to those patients with apparently active tumor in biopsies three to six months after treatment who survived five years. There is probably an indirect radiation effect by the action of the stromal cells on the tumor. They consider that the difference in response by a primary tumor and its lymph node metastasis is a function of the tumor bed.

For purposes of considering the changes within the malignant epithelium after irradiation, Glucksmann⁸ suggested division of malignant cells into four groups, resting, mitotic, differentiated and degenerating. Comparison of these four groups of cells in the normal cervix and in epidermoid carcinoma prior to irradiation was made by Mitra and De²⁸ (Table III). In a series of 91 patients with multiple levels on four biopsies, pretreatment, 7 days after first radium application, 21 days after second radium application and 3 months after third radium application, Mitra and De counted 500 cells from each biopsy and these were grouped into Glucksmann's four standard groups. They found that there was almost a threefold increase in the mean of the differentiated cells over the preirradiation biopsy findings but that this later subsided somewhat to slightly more than the number in the original biopsy. They found that after 7,000 r there was more or less uniform reduction in resting and mitot-

ic cells and an increase in differentiated and degenerating forms. They did not believe that there was any significant variation in this cell population after 7,000 r between the 76 patients who had no cancer cells after 21,000 r and were therefore considered to be radiosensitive and the 15 apparently radioresistant patients in whom cancer still remained.

Glucksmann who believes that radiation leads to differentiation in addition to mutation and degeneration considers that the radiosensitive and radioresistant cancer cells react differently after preliminary irradiation.^{8,11}

The studies of Glucksmann and Spear¹² and Glucksmann and Way¹³ have been concerned with quantitative changes in the cell types of postirradiation serial biopsies. These are taken by the cold knife technique at the growing edge of the tumor at 7, 14, 21 and 28 days following the start of radiation therapy. Such treatment consists of the direct application of radon or radium to deliver a total of approximately 7,500 r followed by deep roentgen therapy. The numbers of the four types of cells are plotted against time in each serial postirradiation biopsy.

A poor or unfavorable response to radiation is indicated by a morphologic picture that is essentially the same as that prior to radiation therapy. Such cases are considered unfavorable in spite of some lessening of mitotic activity, vascular damage or fibrosis of the stroma of the tumor bed. Glucksmann⁹ believes that, while the tumor bed may play some role in the tumor's response to radiation therapy, the essential feature of tumor radiosensitivity lies in the

ability of the tumor to undergo differentiation while being subjected to irradiation.

A favorable response of the tumor to radiation is shown by the elimination of viable cells, *i.e.*, those which are resting or in mitosis. These viable cells have been replaced by increased numbers of nonviable cells; namely, those incapable of undergoing mitosis although still able to differentiate and thence degenerate. Accompanying these changes is an increase in the number of abnormal mitotic figures. A typical favorable response shows, after 7 days, the absence of normal mitotic figures and the reduction of resting cells to less than 30 per cent of the total cell population.

In a series of 100 patients treated by radon and roentgen ray, the clinical follow-up showed that Glucksmann and Spear¹² were 80 per cent correct in estimating that a given tumor would respond favorably to radiation. A histologic prognosis based on serial biopsies made during radium treatment was proved to be correct in 86 per cent of 1,453 patients with cervical cancer. In a series of 466 patients with Stages I and II cervical cancer, the five year cure rate was improved by 14 per cent by operation. This was planned for those patients in whom response was considered to be poor after initial radium treatment. Only those patients who had active cancer in cervix, lymph nodes or both sites two or more months after radium treatment were considered to be surgically cured.¹¹

Jolles and Koller¹⁹ considered that the increase of differentiating cells was apparent after the irradiation since there had been destruction of other cells. Further, they consider that hyperkeratinization of tumor cords after irradiation is abnormal; that is degeneration not differentiation. Using the standards evolved by Warren and associates,³⁴ Kistner and Hertig²¹ found that radiation response of marked degree was accompanied by increased survival.

Further complicating problems are the difficulties in deciding viability of tumor cells and the fact that the biopsy may not

be representative. Martzloff²⁵ found that the preoperative biopsy was not representative of the surgically removed uterus in about one third of a group of cases studied.

There may be a lack of uniform response to irradiation. This does not appear to be related to the source of radiation but rather to the condition of the tumor bed. This is the second very important factor in assessment of radiosensitivity. Warren *et al.*³⁴ considered that the two most important features were the character of this supporting tissue and its degree of vascularity and the presence or absence of infection. It has been postulated that the stromal pattern in specimens obtained prior to any radiation therapy may well be related to the prognosis of the tumor.¹⁸ Indeed, it takes an enormous dose of radiation therapy to kill all cells in a tissue culture; therefore, there must be more to radiation response of a tumor than killing all the tumor cells.³³ Other factors such as the nutritional status of the patient are considered to be important. It has been observed that many normal tissues and some animal tumors appear to have a reaction to roentgen and gamma radiation correlated with oxygen availability; tissues are less sensitive when anoxic at the time of irradiation. This sensitivity is correlated with the availability of oxygen and not with the utilization of oxygen by the cell.¹⁵ This finding has been applied clinically in a small number of cases of carcinoma (other than cervical) considered to be inoperable and hopeless with conventional therapy; the patients having been given oxygen under three atmospheric pressures. The technique is used in the hope that it may improve oxygen tension in that part of the capillary circulation constituting the principal source of oxygen to the tumor cell.⁴

It has been observed by Brack and associates² that the younger the patient the worse the prognosis. They considered that this is related to the advanced stage of the tumor rather than to the age of the patient. On the other hand, in the Connecticut

Tumor Registry⁶ there does not seem to be this same relationship. Indeed, there seems to be a somewhat better prognosis, if anything, in the younger patient. Hormonal influence on radiosensitivity and radiocurability is not understood. Wachtel³² correlated an elevated cornification index after therapy (suggesting high estrogen production) with an unfavorable prognosis. For this reason testosterone and alpha tocopherol have been used¹⁴ to improve prognosis, but there are no definite conclusions regarding the benefit of such therapy.

It has been observed by Glucksmann¹⁰ that premenopausal women with carcinoma of the cervix have more benign cornified cells in the vaginal smear (presumably more estrogenic activity) than does the comparable group of postmenopausal women. Those with persistently high counts of cornified cells during therapy are less likely to do well, suggesting greater estrogenic activity in patients with refractory cancer.

The gross appearance of the tumor may be of great importance since fungating tumors have been observed to have better radiation response than infiltrating tumors.⁵ This may rather be related to the host response influencing the microscopic form taken by the tumor.¹⁷ Furthermore, in all these considerations it is important to remember that the amount of radiation, the size of the field, the rate at which the radiation is delivered and the time between successive doses may play an important part in the ultimate fate of the tumor.

The observations on the types of patients who do well surgically is fairly limited. Bowing and Fricke¹ considered that patients with low grade tumor do well treated surgically, whereas those with a high grade tumor do poorly treated surgically. Nevertheless, their five year cure rate with irradiation was essentially the same for each tumor grade. The numbers treated by surgical techniques with or without the addition of radiation therapy

are too small for statistical evaluation.

Brack and associates² also found a better prognosis in patients with carcinoma in the cervical stump and suggested that such patients report earlier since they know that vaginal bleeding should not occur. There is a lower salvage rate in patients with syphilis, although it is postulated that deaths from syphilis itself may decrease the salvage rate. In the Negro patient the prognosis is worse, and it is suggested that it may be due to reporting at a later stage of disease. Stage for stage there is no difference in prognosis between Negro and white patients.² The results of treatment depend on the virulence of the growth opposed by the resistance of the host and modified by the apparent response of such a tumor to radiation.

Although Kottmeier²³ doubts the existence of radioresistant tumor, he does consider that later surgery may be of limited value in radioresistant cases.

The single most important feature in the prognosis of cervical cancer is the extent of the lesion, that is, the clinical stage.

SUMMARY

There is no uniform agreement as to whether or not histologic examination is of value in determining the form of therapy that should be employed in patients with cervical cancer. Preirradiation tumor grading is prognostically significant in Glucksmann's hands, but Kistner and Hertig²¹ noted no correlation. Glucksmann and Way¹³ found radiation response determined by their standards prognostically significant and also that a 14 per cent better prognosis is obtained for patients with poor response to radiation treated surgically.¹¹ Other workers question their criteria and are unable to produce similar results. Warren *et al.*^{33,34} consider radiation response important but their criteria are different. The problem is further complicated since radiosensitivity does not necessarily mean radiocurability.

It is important to remember that radia-

tion injury is three times as frequent in the good as in the poor response group, although the difference between the two is not fully significant statistically.²²

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CYTOLOGIC PROGNOSIS IN CANCER OF THE CERVIX*

TWO YEAR SURVIVAL RATES IN A RANDOMIZED SERIES

By RUTH M. GRAHAM, Sc.D. (HON.), and JOHN B. GRAHAM, M.D.
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IN ORDER to assess the reliability of the sensitization response (SR) as a prognostic tool in invasive cancer of the cervix, a prospective randomized series has been run. Previous studies were either retrospective¹ or had no randomization.²

The series began in February, 1957, at the Roswell Park Memorial Institute. The first year has been regarded as a trial period for the investigation. It takes some time to organize a randomized clinical study so that everything runs smoothly, particularly when new in an Institution and with an unfamiliar method of radiation therapy. The series reported here is composed of those patients randomized and treated during the second year, from February, 1958 to February, 1959. Stage IV cases were excluded from the randomization. All other cases were included with 2 exceptions—a patient with Stage I cancer of the cervix who was not treated because of an extensive inoperable recurrent carcinoma of the rectum and one with Stage III cancer who had no pretreatment smear.

During the second year, 120 cases were seen. There were 18 in Stage I-small, 16 in Stage I-large, 45 in Stage IIa, 16 in Stage IIb, 16 in Stage III and 9 in Stage IV.

METHOD

Cases were randomized in the following fashion. An SR count was performed on the initial vaginal smear obtained when the patient was first seen in the outpatient department before any pelvic examination was done. The clinical stage was determined by examination under anesthesia. When the SR count and the clinical stage were known, a research nurse opened a sealed

envelope, on the outside of which was a notation as to whether the SR was good or poor and the clinical stage. Inside the envelope a card indicated whether the patient should be included in the radiation series or the study series. In this way, cases were randomized both on the basis of clinical stage of the disease and the cytologic picture.

If the card indicated that the case belonged to the radiation series, the patient received 5,700 rads full pelvis radiation through six portals, 10 cm. × 15 cm. anterior and posterior portals, 8 cm. × 15 cm. lateral portals by a 400 kv. machine in five to six weeks. The radiation dose was constant for all patients, with 2 exceptions, both in their eighties who had radium applications initially. The external radiation was followed by 2,000–3,000 r_r at point A by radium application.

If the card indicated that the patient had good SR—10 per cent or above—and was in the study group, she received radiation therapy as described above. Previous work¹ had indicated that if 10 per cent or more of the benign squamous cells in the vaginal smear were vacuolated basal cells, the cells considered to show the sensitization response (Fig. 1), the patients had a greater five year survival rate if treated with radiation.

If the card indicated that the patient had poor SR—9 per cent or lower—and was in the study group, she received a trial of radiation therapy. Her radiation response was judged to be good or poor at either 1,000 or 2,000 rads. If at 1,000 rads her radiation response was below 25 per cent, it was considered poor, the external radia-

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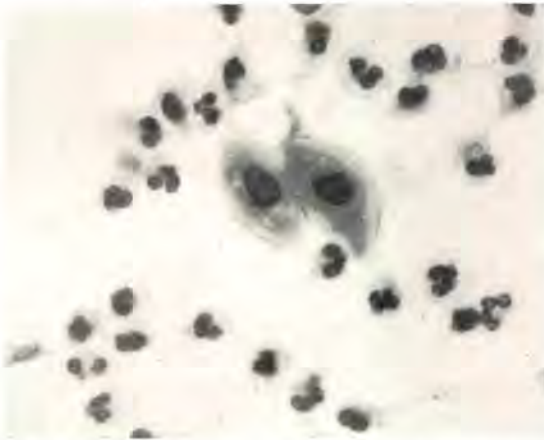


FIG. 1. Basal epithelial cells showing the sensitization response. These cells are characterized by fine vacuolization of the cytoplasm.

tion was stopped and she was admitted for radical surgery. At 2,000 rads the level of radiation response must be above 50 per cent to be considered in the favorable range. There was one group which was an exception to this mode of therapy—patients with Stage I lesions less than 2.5 cm. in diameter with low SR. Previous work² had indicated that this particular group does well with primary surgery.

RESULTS

Comparison of the two groups—the radiation series and the study series—is possible at this time since the cases have been randomized, are comparable in clinical extent of disease and cytologic picture, and have been followed the same length of time—two years or more. No patient has been lost to follow-up.

Though the two series with good SR are identical, it may be of interest to see how comparable the two series are, divided according to their randomization. Table I gives the two year survival rate in Stages I and II. It shows, as might be expected, since these patients have similar clinical extent of disease and cytologic findings, similar results. The over-all two year survival is 90 per cent for the radiation series, and 84 per cent for the study series.

It is in the poor SR group that a dif-

TABLE I
SURVIVAL RATE AT TWO YEARS OF PATIENTS
WITH 10%+ SR

Stage	I	IIa	IIb	Total
Radiation				
Series	4/4	12/13	2/3	18/20—90%
Study				
Series	4/4	10/12	2/3	16/19—84%
Total	8/8	22/25	4/6	34/39—87%

ference might be demonstrated, since here, radical hysterectomy is performed in the study group on those thought to be refractory to radiation. Table II shows the survival rates in these two series. In every stage, the survival rate of the surgical cases is better than that of those given radiation but only slightly. It is perhaps of some interest that in the radiation series 2 of 6 Stage I cases with small lesions (less than 2.5 cm.) succumbed to their

TABLE II
SURVIVAL RATE AT TWO YEARS OF PATIENTS WITH
SR BELOW 10%

Stage	I	IIa	IIb	Total
Radiation	9/12	8/12	0/3	17/28—61%
Study	12/14	7/8	1/6	20/28—71%
(radical hysterectomy)				

disease. In the study series there were 7 Stage I cases with small lesions in which a radical hysterectomy was performed. All are well and without evidence of disease.

Table III shows the correlation between SR and cytologic evidence of radiation response in Stages I and II receiving full

TABLE III
CORRELATION OF SR AND RR

	Good RR	Poor RR
Poor SR 9%—	6	24—80%
Good SR 10%+ 60/67 correlated = 90%	38	1—97%

radiation therapy, *i.e.*, excluding the surgical cases. Of the 39 cases with good SR, only 1 failed to achieve a good radiation response (RR)—an excellent correlation. Of the 30 cases with poor SR, 24 or 80 per cent failed to achieve a good RR. In 60 of 67 cases, there was direct correlation between the initial SR count and ultimate cytologic radiation response.

Table IV gives the two year survival rate in poor and good SR patients—63 per cent and 87 per cent—who received radiation therapy only. This difference is significant at a probability of 0.02. The survival rate in the good and poor radiation response groups shows even a greater difference—88 per cent and 56 per cent which is significant at a probability of 0.01. The difference in the radiation response group is greater than in the sensitization response group. This is explained by the concept that SR indicates a strong probability of the type of response a cancer of the cervix patient will have if given radiation therapy. RR indicates what the response actually is.

The Stage III cases have not been included in the tables since this study was designed to test the efficacy of radical surgery in those patients with poor SR. Patients with cancer of the cervix whose disease has extended and is fixed on the pelvic walls are not amenable to surgical excision. In the study group there were 11 Stage III cases of cancer of the cervix, and 4 are free of disease at two years. In the control group there were 5 cases and 1 is alive. Again the study group shows somewhat better results but the numbers are

TABLE IV

TWO YEAR SURVIVAL RATE IN STAGE I AND II CASES

	Good RR	Poor RR	Total
Poor SR 9%—	5/6	14/24	19/30—63%
Good SR 10%+	34/38	0/1	34/39—87%
Total	39/44—88%	14/25—56%	53/69—77%

TABLE V

DEATHS IN STAGE I AND II CASES

Stage	Ia	IL	IIa	IIb	Total
Good SR					
Study			2	1	3
Radiation			1	1	2
Poor SR					
Study		2	1	5	8
Radiation	2	1	4	4	11

too small to permit evaluation. The only difference in the groups was that the poor SR cases were given alpha-tocopherol during their treatment and the radiation series, placebos. However, since all patients who ultimately had radical surgery also had alpha-tocopherol during their trial of radiation therapy and in no case was any improvement seen, it is unlikely that any improvement in the Stage III cases can be regarded as influenced because of alpha-tocopherol administration. In a previous series³ where the initial radiation treatment was radium rather than roentgen radiation, a significant number of patients appeared to have their radiation response improved by the administration of alpha-tocopherol. This has not been true in this particular series.

There were 24 deaths in the patients with Stage I and II cancer of the cervix. Table V indicates the distribution of deaths according to the series, SR count, and the clinical stage. It is evident from the table that the majority of the deaths are occurring in the poor SR groups—79 per cent. It is also apparent that patients in Stage IIb with poor SR do poorly indeed—whether treated with radiation or surgery. Only 1 patient of 10 survived two years.

That the patient with parametrial extension of her cancer of the cervix—Stage IIb—does poorly if she does not show a cytologic response is indicated by five year figures from Kjellgren⁴ on radiation response. Table VI shows five year survival rates in Stage IIa and Stage IIb cancer of the cervix cases treated by radiation

therapy. There is a difference between the good and poor response in Stage IIA of 22 per cent—certainly a respectable difference. However, in Stage IIB the difference is 50 per cent. It appears that for the patient with parametrial involvement the response of the benign cells to radiation is critical.

CONCLUSION

This study has shown that in a prospective randomized series the number of cells showing the sensitization response is an adequate prognostic method, since it is significant at .02 per cent probability. Radiation response again has been shown to be of prognostic significance. Radical surgery in the poor SR group has been shown to be the equal of radiation therapy but not definitely superior. It is concluded that the responsiveness of the host to radiation is one of the critical factors in controlling the disease.

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TABLE VI
FIVE YEAR SURVIVAL RATE IN STAGE II CASES*

Stage	Good RR	Poor RR	Total
IIA	14/21—66%	10/23—44%	24/44—55%
IIB	23/30—77%	10/38—26%	33/68—49%

* Kjellgren, 1958.

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RADIOSENSITIVITY TESTING OF CERVIX CANCER BY THE TEST DOSE TECHNIQUE*

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THERE is no doubt that the use of radiation or surgical therapy, when employed with skill and experience, can each attain a very high cure rate in cervix cancer of limited extent. Because of the peculiar adaptability of the female reproductive organs to the reception of radium and the high degree of radiosensitivity of cervical cancer, it would seem most logical for all of us to strive for an efficiency rate of our own radiation treatment comparable to that attained in the best treatment centers and leave surgical treatment to those who are unable to reach this ideal. Yet, the renaissance of radical hysterectomy in this country has demonstrated that this mode of treatment may play a therapeutic role for tumors of limited extent in patients of selected surgical quality for those tumors that are relatively resistant to radiation and for those patients whose normal tissues are over-responsive to ordinary doses of radiation.

The problem of clinical radiation resistance is, of course, a complex one and we will finally require the devoted efforts of the radiobiologists to help us understand its basis. This complexity may be gauged to an extent, however, from a brief consideration of the following factors relating to this phenomenon:

1. Problems of variation in dosage with various radiation techniques to central and peripheral areas of the tumor.

2. Variation in the response of tumor cells and the response of the tumor bed. Here the effects of oxygenation and blood supply must play a role on both stromal and tumor cell reaction.^{7,16}

3. Factors of age, general health, habitus and endocrine status of the host.

Our group, like some others, has been interested in a combined therapeutic approach to cervix cancer in an effort to make the surgical and radiotherapeutic modes complementary so that we may provide a treatment specifically suitable for each patient. The study of clinical measurements of host response pioneered by Graham⁸ has proved more complex in our hands than our own study of an index of tumor radiosensitivity defined by cytochemical and cytomorphologic means under test doses of radiation. Host response and tumor response must be closely related and it may be that the tumor response is the cruder end point biologically, and the safer end point clinically. Early tumor response to radiation, however, is surely not the only consideration for radiocurability and we must strive for an understanding of several levels of response for ultimate knowledge in this area.

Throughout the radiotherapeutic era, investigators have attempted to assay the radiosensitivity of cervical cancer by conventional hematoxylin and eosin preparations of serial biopsies under radiation,^{1,14,17} but it remained for Glucksmann⁶ to define tumor cell populations in a meaningful way by his studies of the growing edge of the tumor and his demonstration of the accuracy of his predictions with actual radiocurability or lack of it. His fastidious and accomplished studies suggested the importance of differentiation of tumor cells under radiation and we adhere to this view. Yet this testing program has not been

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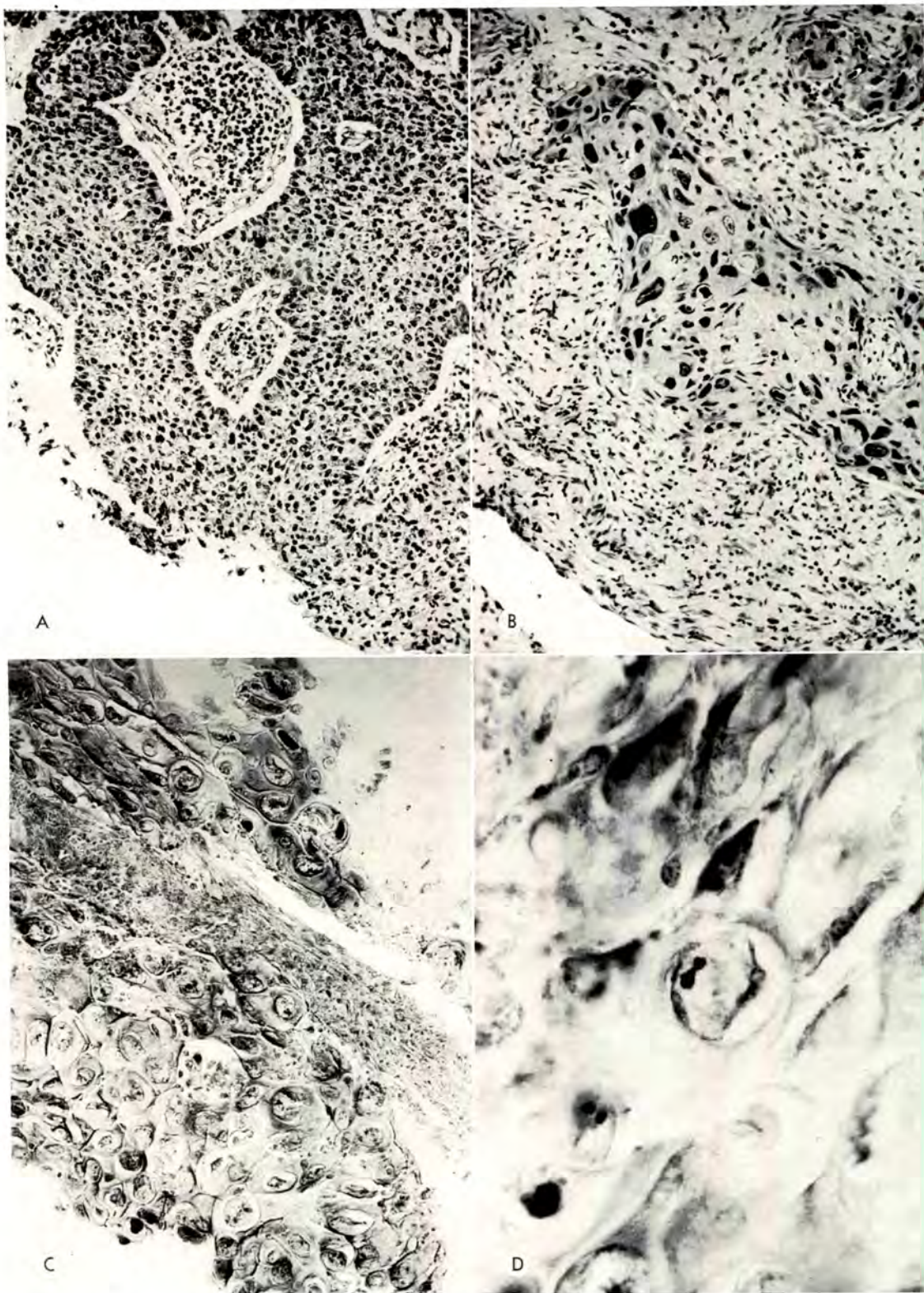


FIG. 1. Tissue sections. RST good. Cancer of the cervix, Stage 1c. Treatment: Transvaginal cone therapy, radium, external roentgen irradiation. The patient is alive and well without disease for four years. (A) H & E, control, $\times 207$. (B) H & E, $\times 207$ (7 days after 3,000 r by transvaginal cone). (C) MGP, $\times 207$ (7 days after 3,000 r by transvaginal cone). (D) MGP, $\times 828$ (7 days after 3,000 r by transvaginal cone).

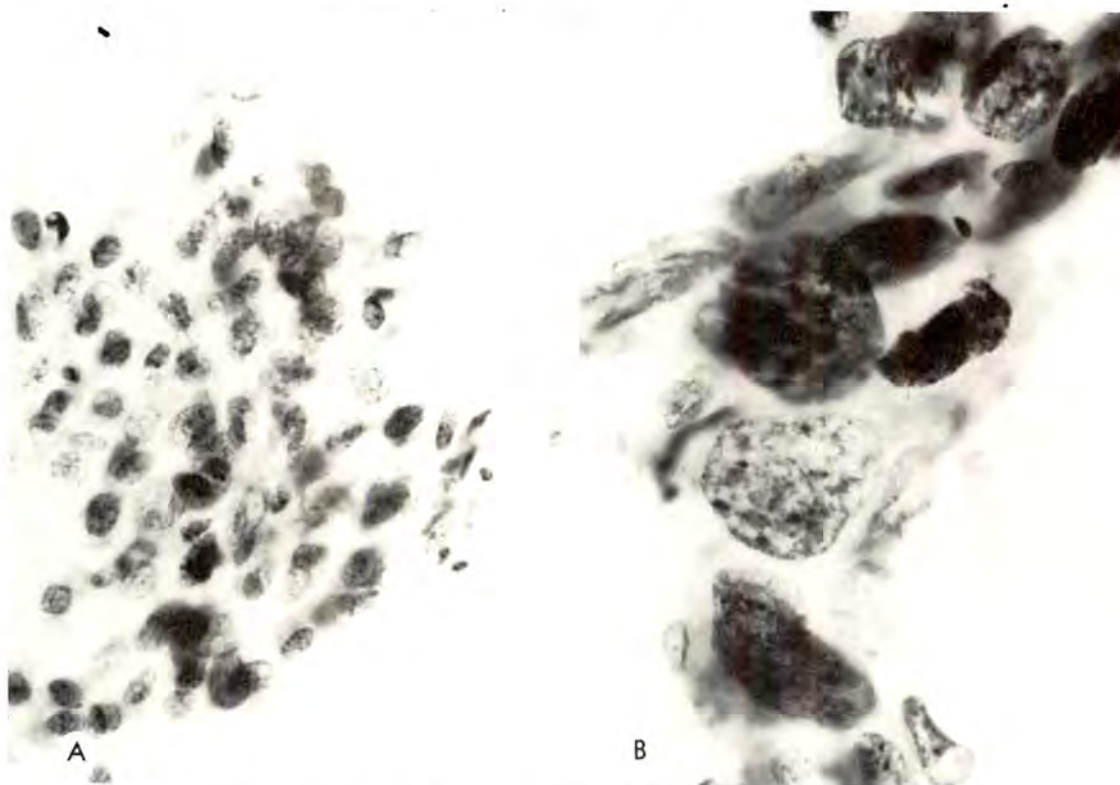


FIG. 2. Same patient as in Figure 1. Cell smears. (A) OFG smear, control, $\times 828$. (B) OFG smear, $\times 828$ (7 days after 3,000 r by transvaginal cone).

widely accepted for: firstly, one hesitates to take the wide block of tissue from the growing edge of the tumor that he demands, lest this incision into the tumor bed interfere with healing, or actually disseminate disease; secondly, the application of a major portion of the radiation treatment in testing is disturbing to many for transfer of the patient to radical surgical treatment after major irradiation may increase the morbidity and mortality rate of a truly radical operation.

TEST DOSE METHOD

We have studied the radiosensitivity and radiocurability (and they must not be considered as synonymous⁴) of cervix cancer by the administration of a small test dose of radiation, given by transvaginal cone. We formerly used 3,000 r (250 kv., 15 ma., 43 cm. target-skin distance, half value layer 2 mm. Cu) in 500 r daily exposures, but we now find 1,600 r in 2×800

r exposures twenty-four hours apart to be equally provocative of a spectrum of response. One may also use external irradiation of 1,600 r tumor dose or a very small application of intracervical tandem radium of the order of 2,000 mg. hours to make such a test, but we have preferred the precision of our standardized transvaginal irradiation; it is superficial therapy which may be virtually disregarded in later radium calculation. Our quadrant control biopsies are obtained beneath the vaginal surface of the tumor in the healthy, actively growing zone, but the growing edge is avoided. Repeat biopsies are then taken one week following the test dose and studied cytochemically and cytomorphologically.^{10,11}

Tissue sections and tissue smears are made from these biopsies and stained for cell population nuclear studies. Orcein fast green is utilized to define the chromatin material, methyl-green pyronin to dis-

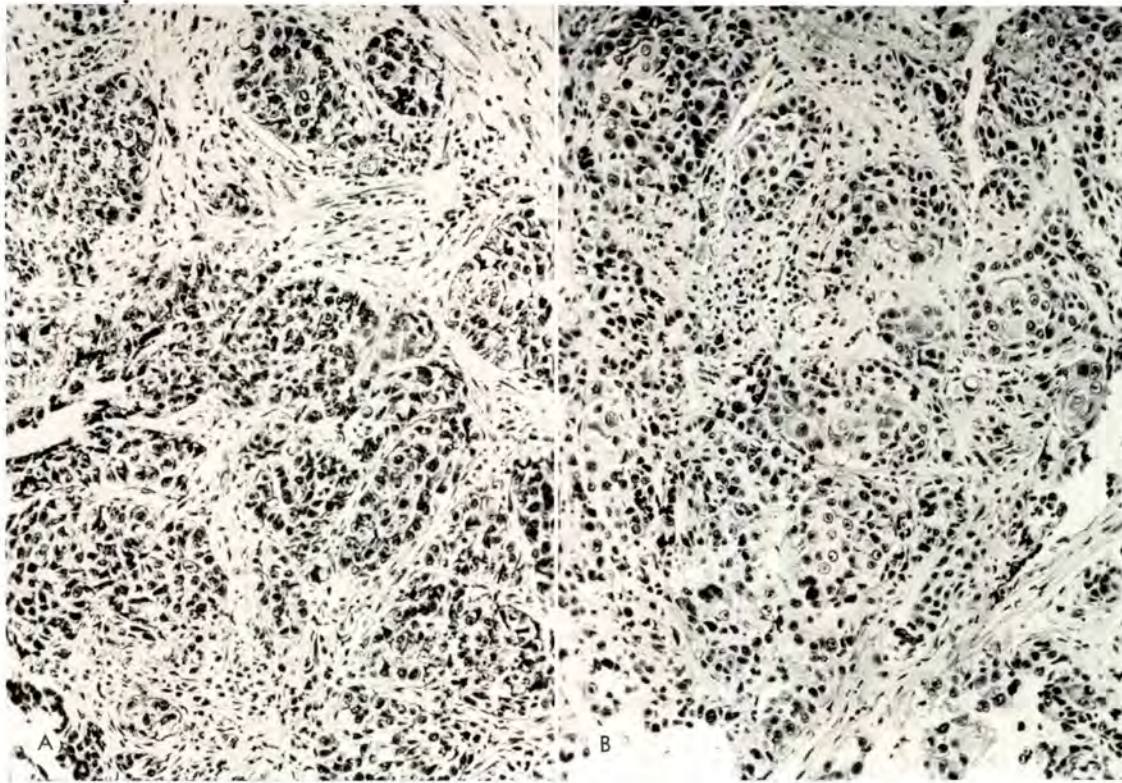


FIG. 3. Tissue sections. RST moderate. Cancer of the cervix, Stage 1c. Treatment: Transvaginal cone therapy, radium, external roentgen irradiation. Died of disease 1 year later. (A) H & E control, $\times 207$. (B) H & E, $\times 207$ (7 days after 3,000 r by transvaginal cone).

tinguish chromatin from nucleolar RNA, Feulgen preparations for precise DNA definition and hematoxylin and eosin for section survey. Once orientation is established in smears, one finds the histologic preparations to be equally usable for clinical testing. Response of 75 per cent or more of the tumor cells indicates a good reaction. The presence of 25 per cent or more of nonreacting, unchanged tumor cells, frequently in the same high power field with reacting cells, is considered a moderate or mixed response, while a poor reaction is indicated by the predominance of unchanged tumor cell nuclei. Most specimens with a good response show virtually 100 per cent reaction and this tumor response is usually accompanied by a striking stromal reaction with the appearance of healthy granulation tissue. We have qualified radiosensitivity tests (RST) good reactions if there was lymphatic in-

vasion in the control biopsies and our analysis of the good response treatment failures suggests the importance of this factor (Table 1).

There are three types of tumor cell reaction indicating responsive reaction to irradiation: (1) death and dissolution of cells; (2) increased differentiation of cells; and (3) radiocytologic reactions indicating the probability of irreversible cell injury such as (a) enlargement of cells and cell nuclei, (b) enlargement of nucleoli (RNA), and (c) alterations in chromatin material (DNA)—apparent early increase followed by relative decline.

Our testing studies^{10,11} are based, in general, on the exploitation of the greater sensitivity to irradiation of the reproductive apparatus of the cell, the chromosomes or DNA, than those relatively insensitive organelles related to protein synthesis and RNA metabolism. This is a rela-

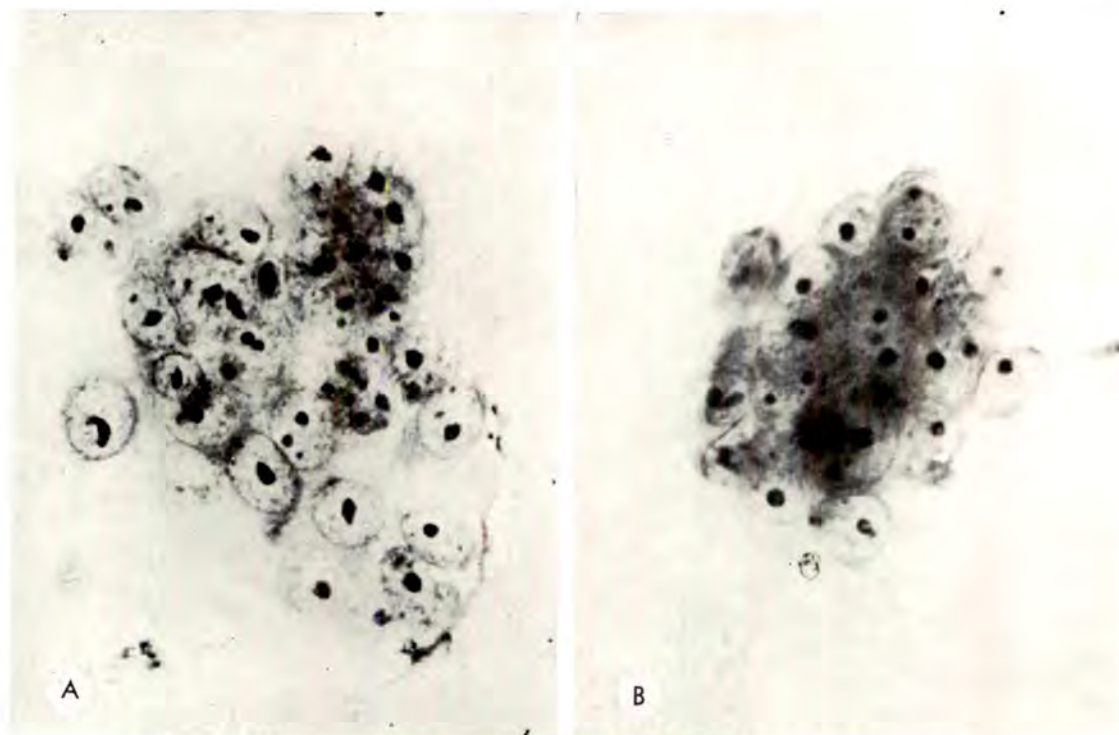


FIG. 4. Same patient as in Figure 3. Cell smears. (A) MGP control, $\times 828$. (B) MGP, $\times 828$ (7 days after 3,000 r by transvaginal cone).

tively crude translation of the work of Caspersson and Santesson,² who demonstrated cytochemically the so-called A and B cell types in tumor: the first a vital, aggressive cell, its nucleus rich in DNA; the second a larger, probably dying cell, relatively poorer in DNA but relatively richer in RNA. The development of their studies³ as well as those of Klein and Forssberg,¹³ Gardella and Lichtler,⁵ and Kelly¹² has confirmed this differential sensitivity of the nuclear components, and it is suggested that interference with mitosis may be a more important factor in the relative DNA rise and decline than is direct chemical effect on DNA synthesis. Richards and Atkin¹⁵ have also studied the relation of mitotic arrest under irradiation to DNA with a similar finding.

Our qualitative, perhaps semiquantitative, cell population studies have enabled us to attain a 70 per cent prognostic accuracy rate in cervical cancers so tested and we have adopted this method for the

choice of treatment in our Stage I and Stage II patients. Our group defines Stage Ia as a microcarcinoma, Stage Ib as a clinical tumor under 2.5 cm. in diameter, and Stage Ic any Stage I lesion over that size. Stage Iia is the conventional designation of a lesion involving fornices and/or proximal parametria and Stage Iib any Stage II lesion of greater extent. All staging is done under anesthesia whenever possible. This radiosensitivity coordinated plan of treatment is shown in Table II. This program favors surgical treatment in Stage I cases except for those with a high radiosensitivity index, and radiation treatment for Stage II cases with the exception of those showing a poor response. Patients with a mixed response, of course, are managed more individually, yet with the same treatment philosophy. It may be noted that approximately 70 per cent of our patients had an excellent response to radiosensitivity testing, while 30 per cent showed a mixed or poor response (Table III).

DISCUSSION

The clinical validity of such a radiosensitivity testing program would seem to require it either to increase the over-all salvage rate in this disease or to provide a technique by which one could choose between two comparably efficient modalities of treatment in clinical situations where such a choice appears logical. There seems little doubt that our method permits us an early selection of those for whom a radiation program is destined to carry a high failure rate (Table IV). Whether or not the substitution of surgical treatment for such patients can offer them a higher promise of cure, we cannot say as yet. Our experience with this method of selection for clinical use is too recent to permit any statistically valid observations on this question, but it

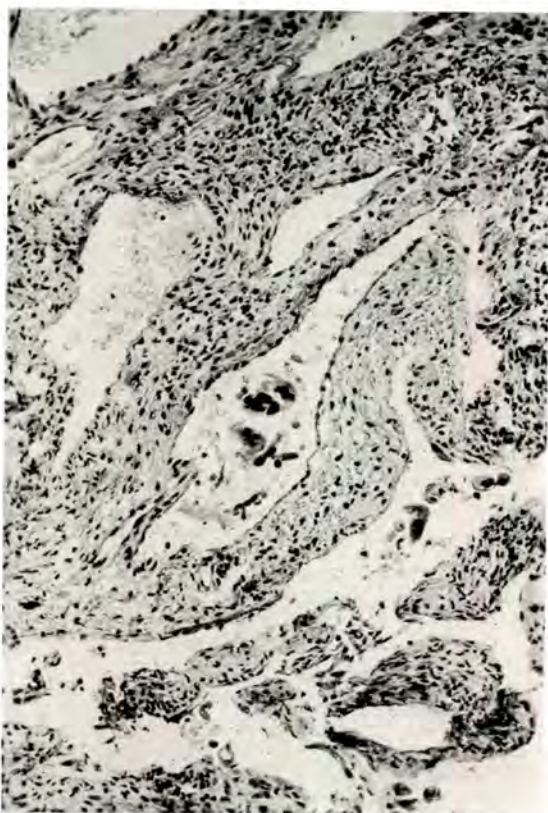


FIG. 5. Lymphatic involvement. RST good. Cancer of the cervix, Stage 1c. Treatment: Radium, external roentgen irradiation. Died of metastatic disease 1½ years later. H & E, $\times 207$. There are tumor cells in a lymphatic of the cervix.

TABLE I
RADIOSENSITIVITY TESTING ROLE
OF LYMPHATIC INVOLVEMENT
IN RECURRENCE
(1961)

Stage	RST Good with Recurrence			RST Good Living and Well	
	No. of Cases	No. with positive lymphatics	Type of recurrence*	No. of Cases	No. with positive lymphatics
I	5	3	M: 2 C: 1	5	0
II	10	7	M: 4 C: 2 U: 1	13	2
III	12	6	M: 2 C: 3 U: 1	9	1
I-III	27	16	M: 8 C: 6 U: 2	27	3

* M = Metastases only.

C = central with or without metastases.

U = site unknown.

is our impression that such tests may disclose tumor virulence as well as radiation sensitivity for we suspect that surgical treatment may also be unsuccessful in these patients (Table V and I). If, however, surgical treatment will attain a higher cure rate than the strikingly poor one seen in the RST moderate and poor group (Table VI), we should be able to increase our over-all salvage rate by a small margin. If, in addition, we can select patients whose normal tissues over-respond to radiation, with the threat of an increased rate of injury (Table VII), we will have provided criteria that will help to define the proper role of radical surgery.

We must bear in mind that generally the majority of patients with Stage I and Stage II cancer of the cervix will be cured with skilled surgical or radiation treatment, but for some the choice of the initial treatment

TABLE II
RADIOSENSITIVITY TESTING AND TREATMENT OF CANCER OF CERVIX
COLUMBIA-PRESBYTERIAN MEDICAL CENTER
(1961)

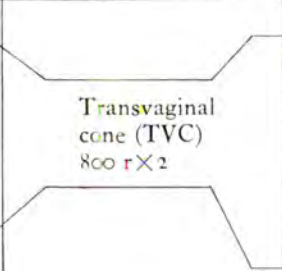
Stage	Test Dose	Treatment
1a-1b	None	Radical Hysterectomy
1c-11a		RST good: radium and roentgen therapy RST moderate or poor: radical hysterectomy
11b		RST good: radium and roentgen therapy RST moderate: second test dose RST poor: radical hysterectomy
III	External roentgen therapy 1,600 r 2,600 r	Continue radiation therapy except in RST moderate or poor cases that are operable

TABLE III
RADIOSENSITIVITY TESTING—CANCER OF THE CERVIX
COLUMBIA-PRESBYTERIAN MEDICAL CENTER
(1961)

	No. of Patients	Per Cent
RST good	98	70.5
RST moderate	31	22.3
RST poor	10	7.2

will be critical. Since by clinical appraisal alone it is impossible to furnish criteria for such a choice or to define the group that requires it, some program of testing seems important to resolve the problems encountered by therapists conditioned to a

unilateral mode of action.

The background for the realization of the shortcomings of clinical selection of patients for surgical or radiation treatment in our hands may be seen in our Stage I results in three treatment eras in our hospital (Table VIII): 1940-1945, when radiotherapy only was used; 1946-1951 when the most favorable patients were selected for surgical treatment; and 1952-1955, when an attempt was made to alternate treatments whenever medically feasible. Without any radical change in the technique of treatment during these periods, we showed a striking variation in the end result.

In Table IX an analysis of recurrences is given of 134 patients on whom radiosensitivity tests were performed.

TABLE IV
RADIOSENSITIVITY TESTING AND CURE RATE
THREE TO TEN YEAR FOLLOW-UP
(1961)

	No. of Patients	Stage I (per cent)	Stage II (per cent)	Stage III (per cent)	Total (per cent)
RST good	63	79.0	63.0	41.2	62.0
RST moderate or poor	29	42.9	13.3	14.3	20.7
Prognostic accuracy	92	73.1	69.0	54.2	66.4

TABLE V

RADIOSENSITIVITY TESTING PATIENTS REFERRED
FOR RADICAL SURGERY
RST MODERATE OR POOR
(1961)

	No. of Patients	Alive and Well
Stage I	3	1
Stage II	2	1
Total	5	2

SUMMARY AND CONCLUSIONS

1. A test dose technique for radiosensitivity testing of cervix cancer is presented, and its cytomorphologic and cytochemical appraisal discussed.

2. The possibility of selecting those patients, one week after a small provocative

TABLE VIII

TREATMENT OF CANCER OF THE CERVIX, STAGE I
COLUMBIA-PRESBYTERIAN MEDICAL CENTER

	Radiation		Surgical	
	No. of Patients	Five Year Cure (per cent)	No. of Patients	Five Year Cure (per cent)
1940-45	87	67.8	0	0
1946-51	41	56.1	60	78.4
1952-55	57	68.5	40	70.0

test dose, for whom a radiation therapy program will probably be unsuccessful offers the promise of admitting surgical treatment of this disease to its proper role.

3. The lack of a method by which the patient with cancer of the cervix can be selected for either radiation therapy or

TABLE VI

RADIOSENSITIVITY TESTING AND CURE RATE
ONE TO TEN YEAR FOLLOW-UP
(1961)

	No. of Patients	Stage I (per cent)	Stage II (per cent)	Stage III (per cent)	Total (per cent)
RST good	98	85.5	66.7	39.2	65.4
RST moderate or poor	36	37.6	16.7	10.0	20.0
Prognostic accuracy	134	79.0	70.0	60.6	70.1

TABLE VII

COMPLICATIONS OF RADIATION TREATMENT
134 PATIENTS WITH CANCER OF THE CERVIX
COLUMBIA-PRESBYTERIAN MEDICAL CENTER
(1961)

RST good:	11 complications (6 with lymphadenectomy)
Genitourinary	3
Genitourinary and gastrointestinal	4
Leg edema	1
Genitourinary and leg edema	1
Hip fracture	2
RST moderate or poor:	1 complication (1 with lymphadenectomy)
Genitourinary	1

surgery, depending on which would most benefit that particular patient, supports the need of some type of a testing program if both of these modalities are to be utilized to their greatest advantage.

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TABLE IX
RADIOSENSITIVITY TESTING ANALYSIS OF RECURRENCE
(1961)

	Total No. of Patients	No. of Recurrences	Metastases only	Recurrences with or without Metastases	Site Unknown
RST good Stage I-III	98	27	12	10	5
RST moderate or poor Stage I-III	36	28	9	15	4

RST good: central recurrence 37.1%.

RST moderate or poor: central recurrence 53.5%.

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OLEIC ACID I¹³¹ INTESTINAL ABSORPTION IN PELVIC COBALT 60 IRRADIATION*

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THE undesirable effects of irradiation have been discussed in numerous papers in the scientific literature dating back to within months of the time when roentgenography was recognized as a clinical tool.^{9,20} In this respect, the gastrointestinal tract has been the subject of a respectable number of reported cases, series studies and experimental works. Dire results from deep radiation therapy range from factitial proctitis² to intestinal deficiency states,⁷ early and late obstruction^{4,11,18} and even to bowel necrosis, perforation and demise of the patient. Interspersed in this volume of reports are writings of investigators seeking interrelations of the associated side effects, such as diarrhea, vomiting³ or intestinal malabsorption. It is these latter studies to which we shall confine our reviews and correlate our observations in the present work.

INTESTINAL REACTIONS TO IRRADIATION

It is not feasible to relate the intestinal changes manifested clinically by radiation therapy patients with those described in association with accidental or experimental single dose high level exposures. It is of interest, however, to note that doses equaling and even doubling the average single therapeutic application to the abdomen will not alter gastric emptying in the dog and doses up to four times the average single daily application will show relatively little evidence of injury, grossly or microscopically, to the stomach of the dog. This is in marked contrast, however, to the extensive injury to the small bowel found on microscopic and gross examination by Conard⁵ and Sullivan *et al.*¹⁹

In a review of the literature, Conard⁶ discusses factors which may possibly favor

the development of diarrhea in irradiated animals. These are: (1) increased secretions from the intestines due to radiation induced denudation of the epithelium, irritation, inflammation and distention of the bowel; and (2) increased or altered bacterial activity which may disturb the normal symbiotic relationship of the bacteria to the host. He points out further that, while the intestinal tract is quite sensitive to ionizing radiation, it also has a most remarkably regenerative and reparative ability. This is evidenced by the finding that doses of well over 1,000 r are required to damage permanently the gut in most mammals studied, and, further, that the bowel is capable of rapid, dramatic recovery of anatomic and functional integrity after doses approaching the lethal range.

Kymographic studies of bowel motility by Conard⁶ demonstrated that roentgen rays increased the motility and bowel tone after doses as low as 100 r, and with larger doses this tone increased further and the duration of response was longer.

Mead, Decker, and Bennett¹⁴ described a tendency toward increased tone and motility of the gastrointestinal tract after irradiation, resulting in retention of oil in the stomach or rapid passage past the absorbing intestinal surface. In their experience, fat absorption *per se* appeared normal and in some cases increased. They concluded that there was no evidence of postirradiation impairment of fat absorption in rats receiving 600 to 700 r whole body irradiation. British and American authors as early as 1924 discussed changes in intestinal fat absorption incident to irradiation. Dodds and Webster⁷ observed an immediate increase in fecal neutral fat

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content in the stool during irradiation of the abdomen and spleen. This did not occur when other more remote parts of the body were treated. Martin and Rogers¹³ isolated loops of dog intestine and described malabsorption of fat from these loops following exposure to ionizing radiation. Their observations were based on the failure of the mesenteric lymphatics to visualize after a fatty meal was given to the postirradiated dog. In support of these observations, Buchwald¹ found diminished absorption of the sugars, dextrose, fructose and mannose in rats twenty to forty hours after exposure to sublethal levels of irradiation.

An extensive, comprehensive discussion of the microscopic changes of tissues and cells of the intestinal tract is incorporated in a review by Friedman.⁸ He observed that the absorptive behavior of the intestine after abdominal irradiation showed pronounced alteration. In the more recent literature, Moss¹⁵ has pointed out the effects of ionizing radiation on the absorption of sugars, describing depression of absorption in the postirradiated rat as compared with absorption levels in control animals. Reeves and co-workers¹⁷ reported changes in the intestinal absorption of labeled fat and fatty acid associated with abdominal therapy using orthovoltage equipment. In their study slightly less than 50 per cent of their patients demonstrated transient decreased fat or fatty acid absorption during irradiation.

Our observations in the past led us to believe that the incidence of diarrhea, nausea, vomiting and weight loss in patients receiving cobalt 60 teletherapy was somewhat lower than that observed with orthovoltage therapy. We chose to evaluate this observation using the oleic acid I¹³¹ intestinal absorption technique.

PATIENT SELECTION AND RADIATION TREATMENT PLAN

Forty-eight patients accepted for routine irradiation for carcinoma of the cervix made up this study group.

Staging of the neoplastic lesion in

accordance with the League of Nations classification determined the dosage to be applied to Points A and B in the parametrium. Table I shows the plan of irradiation

TABLE I
IRRADIATION PLAN

No. of Patients	Stage	Co ⁶⁰ Teletherapy Dose at Point B (r)	Ernst Radium Applicator Dose at Point B (r)	Total Dose (r)
9	I	3,500	1,610	5,110
25	II	4,000	1,800	5,800
8	III	4,000	1,800	5,800
6	IV	3,500	—	3,500

employing cobalt 60 teletherapy and radium loaded Ernst applicators. Thirty-three patients (Stage II and III) in the series were treated to approximately equal dosage levels with identical techniques. Figure 1A illustrates the arrangement of the two 6×14 cm. anterior and posterior ports for Stage I, II and III lesions. Stage IV lesions received the external irradiation through single 15×18 cm. anterior and posterior ports (Fig. 1B). Intracavitary radium was rarely applied in Stage IV cases. Figure 1C illustrates the relationship of the Ernst applicator to the irradiation portals for treating Stage I, II and III lesions.

The barium seen in Figure 1, A, B and C partially outlines the small bowel lying in the treatment fields. The volume of intestine exposed to radiation is recognized as variable, not only from patient to patient but also in the individual patient from treatment to treatment. In a human study this variable cannot be avoided or corrected, however.

METHOD

An intestinal oleic acid absorption study is performed prior to the first radiation treatment period in order to establish a baseline for each patient. A second evaluation is carried out at midtreatment after the delivery of approximately 1,700 to 2,000 r to Point B. The third absorption study is performed on the day of comple-

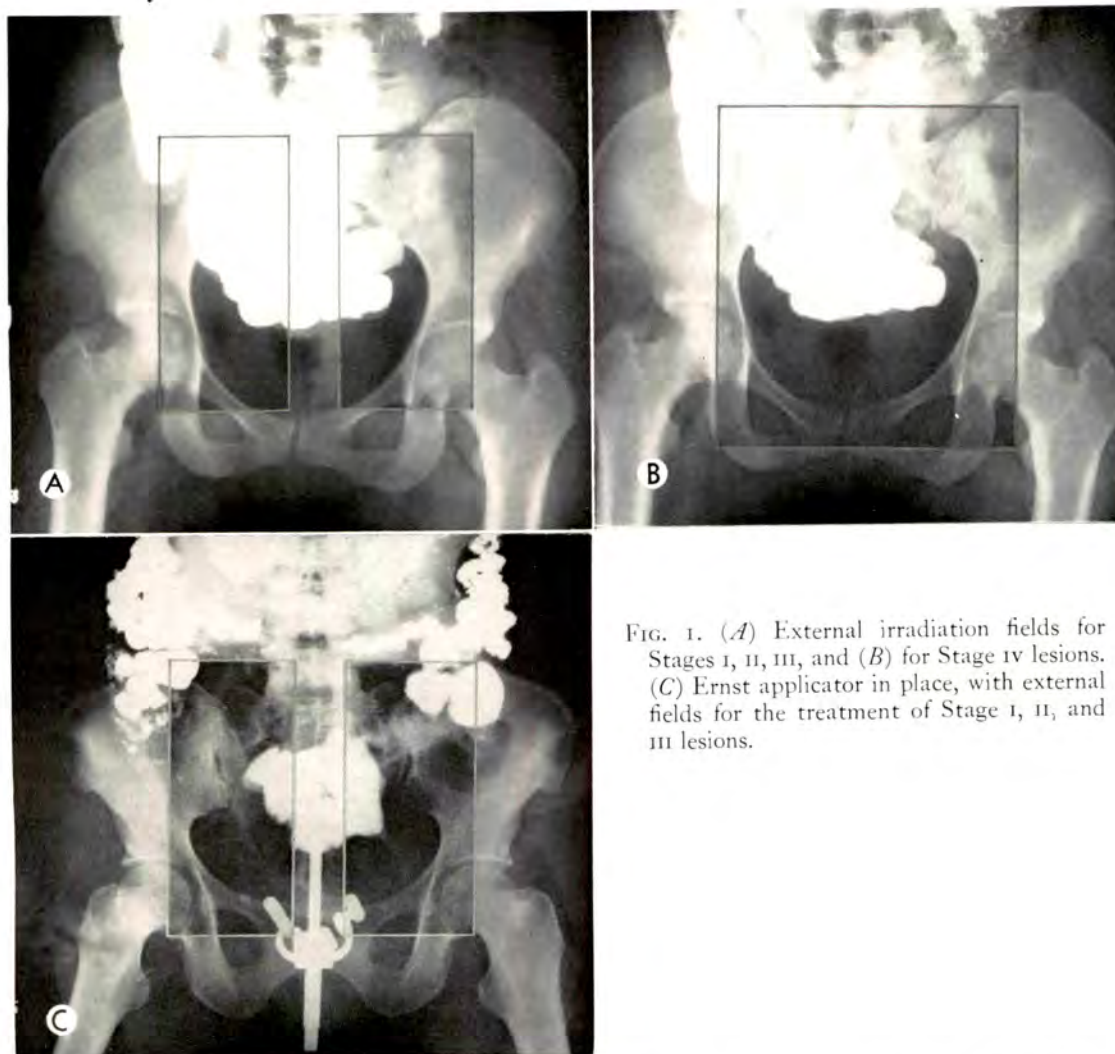


FIG. 1. (A) External irradiation fields for Stages I, II, III, and (B) for Stage IV lesions. (C) Ernst applicator in place, with external fields for the treatment of Stage I, II, and III lesions.

tion of cobalt 60 teletherapy with approximately 3,500 to 4,000 r having reached Point B. Intracavitary application of radium by Ernst applicator follows the cobalt 60 irradiation within a period of approximately two weeks. Follow-up absorption studies are performed at an average of eight weeks after cobalt 60 teletherapy to determine whether delayed depression of absorption has occurred or whether, in patients with abnormal results during or on completion of therapy, there has been a return to normal.

TECHNIQUE

Patient Preparation. On the day before each absorption study, the patients ingest 15 drops of Lugol's solution with each

meal in order to provide a thyroid blockade. After the evening meal nothing is taken by mouth. On the morning of the fat absorption test, the dosage capsules of I^{131} labeled oleic acid are given with the dietary prepared test meal which contains 20 gm. of fat and consists of cream and milk, cereal and coffee or tea.

Dosage and Standard Preparation. Doses of I^{131} oleic acid in the amount of $50 \mu\text{c}$ and in volumes averaging 1 to 1.5 cc. are prepared by diluting the acid with olive oil. This is placed in size 00 gelatin capsules. The oil has no effect on the gelatin and leakage has not been noted, even after long periods of standing. This same measured dose is diluted by volume, 1:10,000, using petroleum ether for the standard solution.

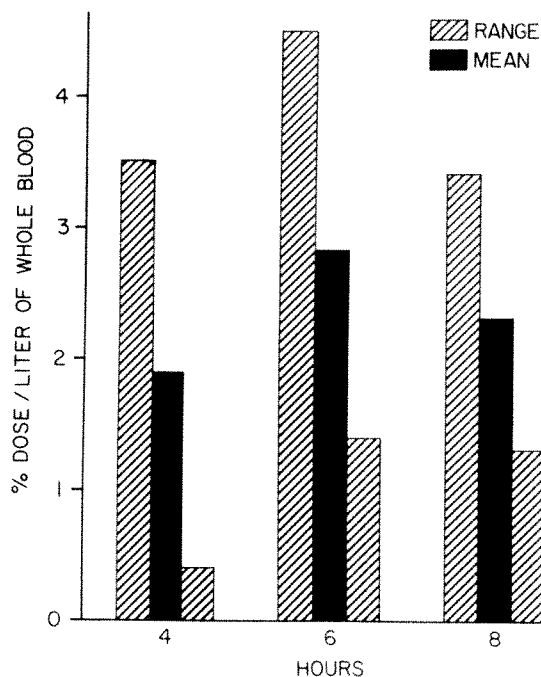


FIG. 2. Normal baseline absorption results. Range and mean of oleic acid I^{131} absorption in 36 subjects. The studies were performed one day prior to the initiation of Co^{60} therapy.

Sample Collections, Counts and Calculations. Whole blood samples are collected in heparinized tubes at two, four, six, eight and twenty-four hours. The usefulness and reproducibility of studies employing urine and stool samples have been of little value in our experience. The reproducibility of the blood sampling technique has been shown by Isley and co-workers.¹⁰ Two cc. aliquots of whole blood are pipetted into counting tubes and the activity is measured in the scintillation well counter. The recorded counts are compared with measurements of an equal volume of the standard solution and the result is expressed as a per cent of dose per liter of whole blood. The minimum values of normal were set in accordance with the values proposed by Kaplan and co-workers.¹² No abnormality was interpreted for the high level ranges found in a few subjects of this group. Figure 2 illustrates the wide range of normals observed in the oleic acid I^{131} absorption studies of this group.

RESULTS AND DISCUSSION

Although the occurrence of diarrhea during irradiation was a strong stimulus for this study, there is no evidence to show that intestinal absorption of fats is related to or influenced by diarrhea. Actually, a low incidence of clinical diarrhea was observed in the 48 subjects studied. In the 15 subjects having diarrhea, normal absorption patterns were maintained by 12. It is suspected that diarrhea reflects the effects of irradiation on the large bowel rather than on the small intestine. This is supported by the lack of correlation between the intestinal absorption results and the incidence of diarrhea.

The factor of weight loss has also assumed a more optimistic aspect in this study. Figure 3 illustrates the narrow differential between the average gain and loss of weight in the subjects of this group during the course of therapy. A single patient who followed a downhill course throughout therapy accounts for the high value for weight loss in the follow-up column. A number of patients at follow-up had gained in excess of 10 pounds, thus accounting for the small differential between the mean values of the two columns. This finding is explained clinically, we believe, on the basis that, in some, a loss of several pounds is the result of the various degrees of nausea and anorexia associated with irradiation; on the other hand, a gain in weight follows the frequent general improvement in the soma and sensorium of

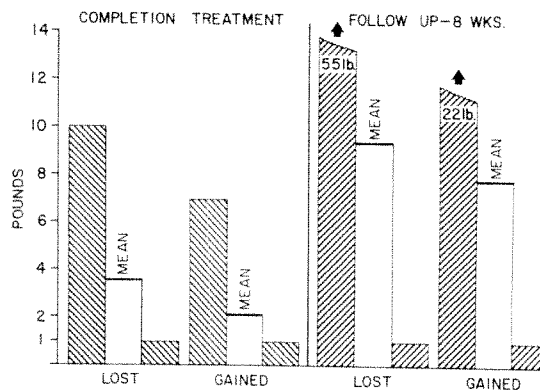


FIG. 3. Weight changes, showing range and mean.

patients as bleeding and discharge cease and bulky, toxic tumors regress in size and symptomatology.

Twelve patients in this series had abnormally depressed baseline absorption (Fig. 4). Five of these actually showed improvement of intestinal absorption as cobalt 60 therapy progressed and only 1 patient showed further depression of absorption on completing therapy. The remainder showed no change in the already low absorptive levels throughout the series of treatments.

In the group of 36 patients having normal baseline absorption studies, 8 exhibited abnormally low absorption levels at midtherapy or at completion. On the other hand, 7 patients in the normal baseline group showed less than 1 per cent variation from the baseline value during treatment. This accounts for the minor degree of variation between the mean absorption values found at midtreatment and at completion of therapy (Fig. 5). The results in the remaining 29 normal baseline subjects having greater than 1 per cent increased or decreased absorption from base levels are graphically presented in Figure 6. At midtreatment, 18 subjects had increased absorption levels and 11 exhibited a decrease; 9 maintained below baseline absorption levels during cobalt 60 therapy, while 11 maintained

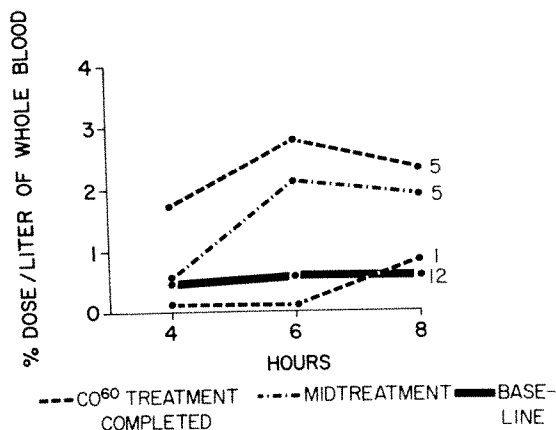


FIG. 4. Absorption results in 12 patients having an abnormal baseline. The curves represent the mean values for the number of patients indicated at the end of each line.

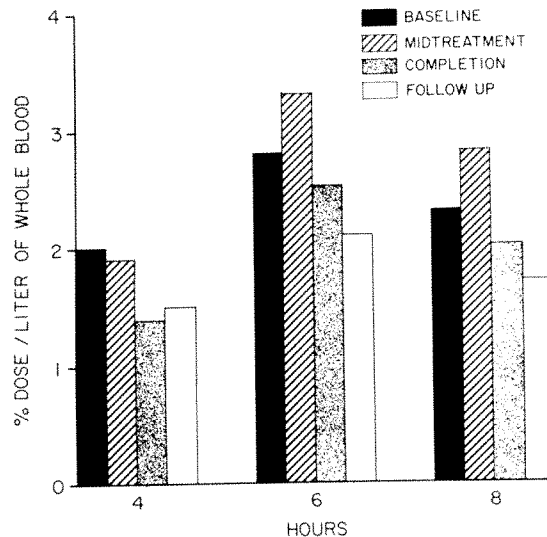


FIG. 5. Serial bar graphs showing the mean values of absorption in 36 subjects with normal baseline who completed Co⁶⁰ therapy and 21 of whom were followed for eight weeks after Co⁶⁰ irradiation.

above baseline absorption levels during this period. From this one would conclude that no consistent change in intestinal absorption occurs during cobalt 60 pelvic irradiation.

Twenty-one patients examined at an average of eight weeks following completion of cobalt 60 therapy account for the slightly increasing variation from the baseline in Figure 5. Five subjects in this group had abnormal levels of absorption. Of particular interest is the observation that 4 of these had maintained normal levels throughout the period of therapy. Conversely, 3 subjects having normal levels at the eight weeks' follow-up had shown abnormal absorptive levels during treatment. Figure 7 illustrates the mean absorption curves for the subjects varying more than 1 per cent above or below the original baseline findings. It would appear that an increase in the incidence and degree of absorption depression has occurred at the time of the follow-up study. This, we believe, reflects the expected delayed effects of cobalt 60 irradiation on the intestine.

We recognize that at this time accurate statistical evaluation is impossible because of the small number of patients. From this series, however, one can postulate that, in

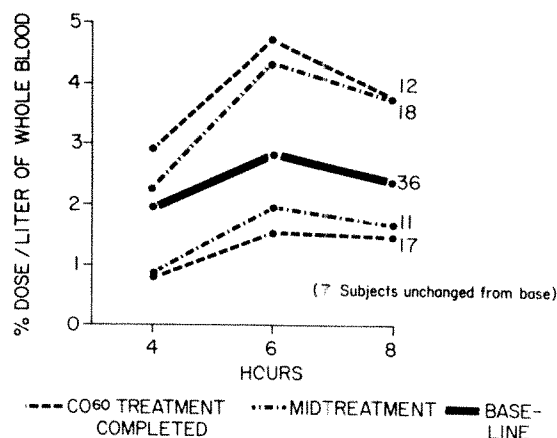


Fig. 6. Line graphs showing the average values of oleic acid I^{131} absorption at designated intervals during Co^{60} irradiation. Seven subjects showed less than 1 per cent variation from the baseline throughout the treatment period. The numerals at the end of each line indicate the number of subjects varying 1 per cent or more from the baseline.

the early phase of treatment with the application of 1,700 to 2,000 r to Point B, there is, in some cases, an augmentation of intestinal absorption. This may be the result of increased intestinal vascularity or perhaps of prolongation of intestinal transit time. An explanation for the appearance of early depression of absorption may lie in the converse of this statement. Either condition may exist according to individual variation.

Of particular significance, however, is the low incidence of depression to abnormal levels. This relates to at least one important clinical aspect. The maintenance of good nutrition is recognized as a most important factor from the standpoint of efficacy of therapy and also of postirradiation recovery. Therefore, the absorption of fats is of definite value and, in this study, we have shown little alteration of absorption and no evidence of irreversible change during the time intervals studied.

Realizing that the full extent of the effects on tissue from ionizing radiation may not appear for six months or longer,¹⁶ it is our intention to extend this study. Protracted follow-up examinations will be made in an effort to determine the incidence and degree of intestinal malabsorp-

tion of fats in patients receiving deep pelvic irradiation.

SUMMARY

Periodic oleic acid I^{131} intestinal absorption studies have been carried out at pre-planned intervals during the course of pelvic irradiation of 48 patients having a diagnosis of carcinoma of the cervix. Twenty-one of these patients, followed for a period of eight weeks after cobalt 60 irradiation, have provided follow-up studies.

Evaluation of these absorption studies indicates that a very low incidence of depression to abnormal levels occurs during therapy, at completion of treatment, or at eight weeks after cobalt 60 irradiation. These findings appear somewhat contrary to those in the majority of earlier reports. One can hypothesize that this negative finding may be related to the tissue sparing effect of cobalt 60 gamma radiation as compared to the effects of the heterogeneous beam generated by orthovoltage equipment and utilized in prior clinical studies.

Extended follow-up studies are planned for evaluation of any delayed effects

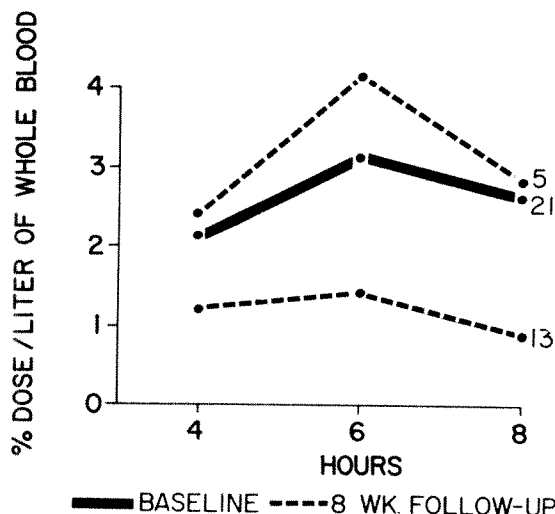


Fig. 7. I^{131} oleic acid absorption results eight weeks after Co^{60} therapy. The mean values for patients varying 1 per cent or more from the baseline are shown. The numerals at the ends of the lines indicate the number of patients. Three patients showed less than 1 per cent variation from the baseline.

incident to cobalt 60 teletherapy, and it is also proposed to study the intraindividual and interindividual range of normal fat absorption in nonirradiated individuals.

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ADDENDUM

Since the acceptance of this paper for publication, additional post-treatment oleic acid I¹³¹ absorption studies have been performed on the above group of patients. Thirty-eight patients have now been studied at 8 weeks post therapy, 34 at 19 weeks and 22 at 31 weeks. The follow-up evaluations were terminated when 12 of the subjects appeared for study at 43 weeks post therapy.

The absorption results of each group were subjected to statistical analysis using the Student T test for the level of significance of deviation from the baseline. No statistically significant alteration of intestinal fat absorption occurred during therapy, on completion of treatment or at intervals of 8, 19, 31 and 43 weeks post therapy. The mean value of the baseline study agreed with values of normal published in the literature, and the variation of one standard deviation above and below the mean coincides closely with the published range of normal. It is felt that sufficient time has elapsed during the study period to encompass any anticipated delayed effect which might be mirrored in the fatty acid absorptive capacity of the intestine.

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MAMMOGRAPHY OF BREAST SARCOMA*

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SARCOMA of the breast is uncommon, comprising less than 1 per cent of all mammary malignancies. Botham *et al.*,² at the Mayo Clinic, report 1 sarcoma to every 100 mammary carcinomas. Of approximately 500 malignant lesions of the breast studied roentgenographically by us, 3 primary sarcomas and 4 metastatic lymphosarcomas of the breast were found.

Sarcoma may arise in the fibrous tissue of the breast or in the fibrous tissue of a fibroadenoma.⁷ Cases have been reported which illustrate the growth of spindle cell sarcoma in the wall of a cyst, but more frequently sarcoma arises from an intracanalicular fibroadenoma. The gross appearance is that of a well-circumscribed, partially or wholly encapsulated growth with lobulation of the exterior surface. The cut surface is smooth, glistening, firm and may be homogeneous or whorled.

In the Mayo Clinic study,² primary sarcomas occurred in the following order of frequency: (1) fibrosarcoma, (2) rhabdomyosarcoma, (3) osteogenic sarcoma, (4) malignant mixed tumor of the breast, (5) malignant fibrosarcoma and carcinoma, and (6) liposarcoma.

Peripheral encapsulation, which so frequently occurs, appears both roentgenographically and grossly as a distinct feature, and consists of primary tumor cells which are compressed, flattened and concentrically arranged. However, in the more anaplastic lesions, the areas of pseudo-encapsulation are less evident, with a tendency towards invasion of the contiguous mammary tissue or musculature.

REPORT OF CASES

CASE 1. C945, a thirty-nine year old female, was admitted to the hospital with a large nontender mass in the upper outer aspect of the left breast, present to the patient's knowledge for

only two weeks. A physical examination performed nine months previously revealed no masses. There were no appreciable skin changes and the axilla appeared normal.

Roentgen examination (Fig. 1) revealed a single nodular mass with indistinct margins measuring 3 cm. in diameter without any evidence of adjacent infiltration. The possibility of medullary carcinoma was suggested.

The pathologist described a soft mass with no appreciable capsule, irregularly spherical, measuring 3 cm. in diameter. A medullary carcinoma was thought to be present at examination of the frozen section, but the paraffin



FIG. 1. Case 1. A thirty-nine year old female with a single nodular mass in the upper outer aspect of the left breast. There is no evidence of adjacent infiltration. Diagnosis: fibrosarcoma.

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section was identified as fibrosarcoma. The axillary lymph nodes were not involved.

CASE II. C1096, a seventy-three year old female, noted a non-tender mass in the left breast five days previous to her admission to the hospital. A large mass was palpable, somewhat irregular and firm, and measured 4×3 cm. in diameter.

The roentgen examination (Fig. 2) revealed a circumscribed mass, with no evidence of skin involvement or adjacent infiltration. A possible diagnosis of medullary carcinoma was suggested.

The biopsied tissue was reported by the pathologist to be a fibrosarcoma, possibly arising from a fibroadenoma. There was no lymph node involvement.

CASE III. C1413, a fifty-eight year old female, noted a large non-tender mass in the right breast six weeks prior to physical examination. A mass $2 \times 2\frac{1}{2}$ cm. was found in the axillary tail of the breast; it extended into the axilla and felt hard and smooth. There was no skin reaction.

The roentgen examination (Fig. 3) revealed a sharply circumscribed rounded mass which was believed to be a benign fibroadenoma.

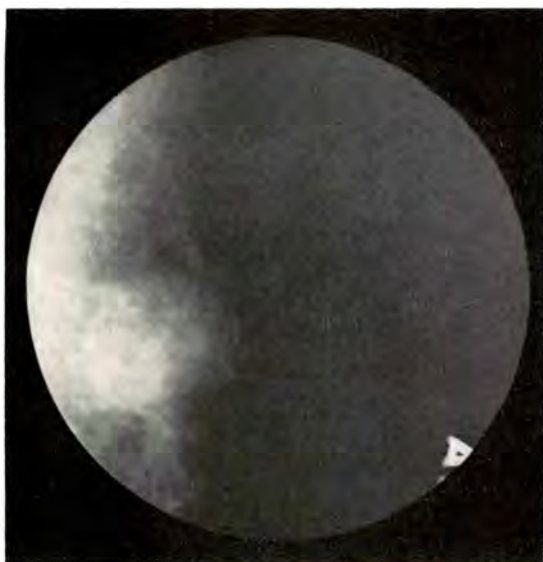


FIG. 2. Case II. A seventy-three year old female with a circumscribed mass in the left breast and with no evidence of skin involvement or adjacent infiltration. Diagnosis: fibrosarcoma, possibly arising from a fibroadenoma.

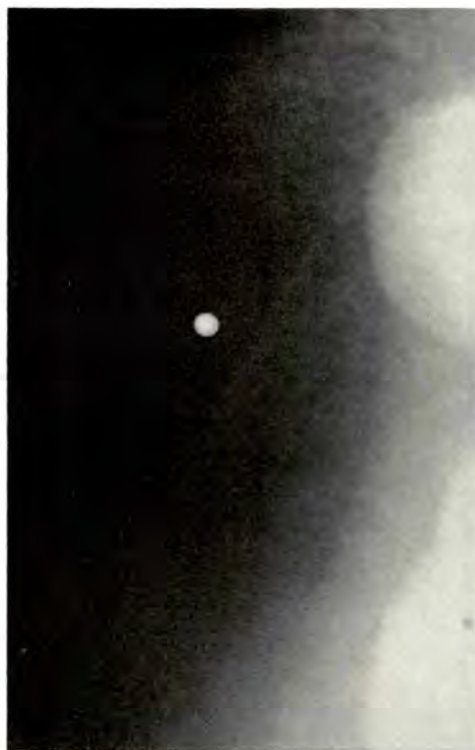


FIG. 3. Case III. A fifty-eight year old female with a sharply circumscribed mass in the upper outer aspect of the right breast. No skin or subcutaneous infiltration is present. The marginal outline of the mass suggests a fibroadenoma. Diagnosis: lymphosarcoma.

A well-encapsulated mass 2 cm. in diameter was removed by the surgeon and was reported by the pathologist to be a lymphosarcoma. There was involvement of the adjacent pectoral and axillary lymph nodes.

CASE IV. C3324, a forty-seven year old patient, was admitted to the hospital with a diagnosis of widespread metastatic involvement of the lung fields and abdomen with ascites and an enlarged liver. She had been aware of a mass in the left breast for the past twenty years. Physical examination revealed a hard, freely movable nodule measuring $1\frac{1}{2} \times 2\frac{1}{2}$ cm. in diameter behind the left nipple.

The roentgen findings (Fig. 4) showed an irregularly marginated mass behind the left nipple, diagnosed as a possible malignancy.

Biopsy revealed a lymphosarcoma.

CASE V. C3892, a forty-one year old female, noted a non-tender mass in the left breast for the first time four months after a negative phys-



FIG. 4. Case IV. A forty-seven year old female with an irregularly margined mass behind the left nipple regarded roentgenographically as a possible malignancy. Diagnosis: lymphosarcoma.

cal examination. A firm mass, freely movable, non-tender, and measuring 2 cm. in diameter was found in the upper outer quadrant of the left breast. There was no evidence of adjacent skin fixation or axillary lymphadenopathy.

Roentgen studies (Fig. 5A) indicated a fairly well-defined, dense, soft tissue mass which appeared to be a fibroadenoma.

The mass removed by the surgeon was 2½ cm. in diameter—lobulated in appearance—and, upon gross examination, was thought to be benign. The pathologist reported this lesion to be a markedly hyalinized and edematous fibroadenoma.

The patient returned four months later with a recurrent mass at the site of the previous operation. A firm, movable, non-tender mass was found measuring 5×6 cm.

The roentgen examination at this time (Fig. 5B) again revealed a mass similar to the previous study in all details except that it was considerably larger. The pathologist described the mass as active proliferating dense scar tissue, but still primarily a fibroadenoma.

The patient was again readmitted to the hospital three months later with a recurrent mass at the same site. The pathologist at this time reviewed the previous slides and felt that they suggested the possibility of fibrosarcoma. A simple mastectomy with excision of a portion of the pectoralis major was performed and the pathologist made a final diagnosis of fibrosarcoma.

CASE VI. C4588, a forty-nine year old female, had had a biopsy of a breast mass two years previously which was diagnosed as lymphosarcoma. In February of 1959, extensive lymphadenopathy and hepatomegaly were noted. She was treated with leukeran and her general response was excellent. She had an exacerbation of symptoms and was again treated with leukeran with no appreciable improvement. In August of 1960, the patient reported a mass in her right breast.

The roentgen study (Fig. 6A) revealed a very well-defined mass in the right breast. Although we had felt that this configuration was suggestive of a cyst or fibroadenoma, we suggested the possibility of a well-circumscribed lymphosarcoma. A course of roentgen therapy was proposed both for its diagnostic and therapeutic value. The mass disappeared following the administration of 1,000 rad delivered with cobalt 60 radiation which was sharply collimated to the area of the mass. Repeat mammography (Fig. 6B) confirmed the clinical impression that the mass had completely responded to therapy. However, a new mass, not present previously, was identified at this time. Another course of cobalt therapy was initiated at this site and the response again was dramatically good. It is now one year since her last treatment and no further involvement has occurred.

CASE VII. C4839, a forty-eight year old female, was admitted to the hospital with a diagnosis of generalized lymphosarcoma. She responded well to chemotherapy initially, but gradually became resistant both to corticoids and chemotherapy.

The roentgen findings (Fig. 7) showed extensive bilateral axillary lymphadenopathy

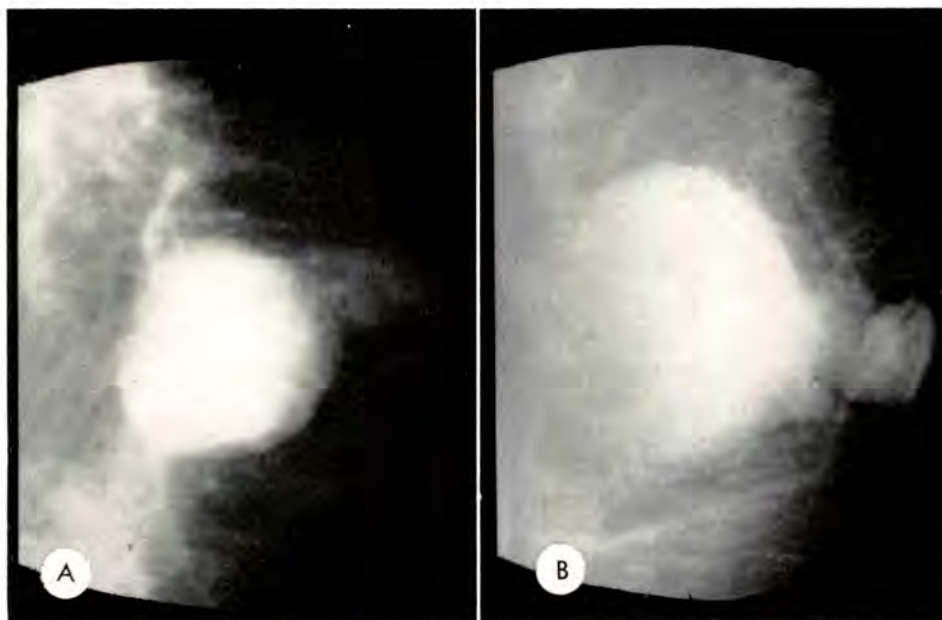


FIG. 5. Case v. (A) A forty-one year old female with a fairly well-defined mass in the left breast which was roentgenographically consistent with the appearance of a fibroadenoma. (B) The mass recurred four months after removal and was roentgenographically and microscopically considered as recurrent fibroadenoma. When the mass recurred a third time, three months later, all the slides were reviewed and the lesion was re-interpreted as fibrosarcoma.

and an intramammary sharply defined mass in the upper outer aspect of the left breast which was shown to be an area of lymphosarcoma. This patient expired of widespread disease shortly after we saw her.

DISCUSSION

All of the cases cited above showed a similar roentgen appearance—whether primary sarcoma, such as fibrosarcoma, or generalized lymphosarcoma with mammary involvement. Each of the lesions was strikingly dense and well margined and there was no evidence of invasive or infiltrative activity. The irregular, spiculated, marginal outline characteristic of scirrhous carcinoma was not present in any of these cases.⁹

Another striking feature was the increased tissue density. This was evidenced to such a degree that, even in those breasts in which mazoplasia and adenosis were also present, the sarcomatous masses were easily discernible and differentiated; by

contrast, some carcinomas are similar in density to the surrounding tissue and may not be so readily apparent.^{1,9}

The rapidity of the growth of sarcomas was still another striking feature⁸ (Cases v and vi). Serial roentgen studies over a period of several weeks revealed such rapid growth that the possibility of an inflammatory collection in an abscess or the accumulation of fluid in a cyst had to be eliminated. This rapid growth rate contrasts strikingly with that observed in cancers previously reported by us.³

Another feature of sarcomas was the extremely well-defined marginal outline. In lymphosarcoma, this feature was practically indistinguishable from the sharp marginal outline of a benign cyst.⁴ Fibrosarcoma, on the other hand, while well margined, tends to be minimally irregular and lobulated like fibroadenoma.

With sarcomas, the measured physical size and the measured roentgen size are approximately the same. This is in contrast to carcinomas, where the physical size

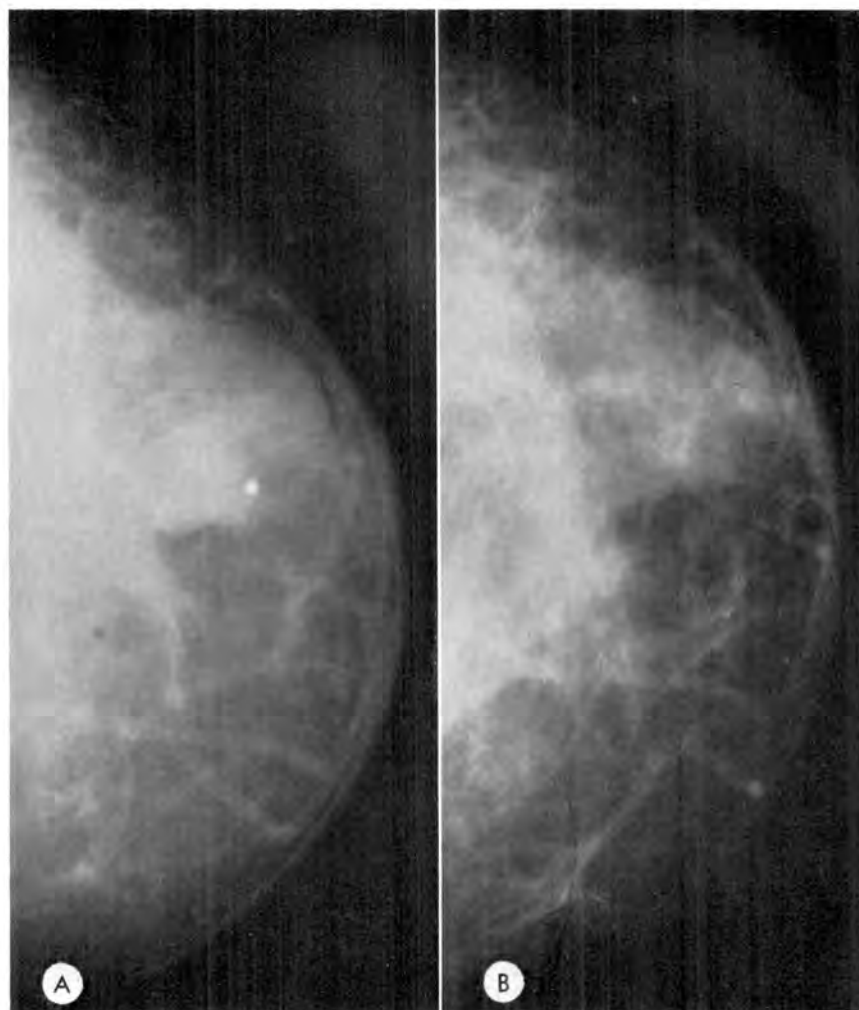


FIG. 6. Case VI. (A) A forty-nine year old patient having a very well-defined mass in the right breast with generalized lymphosarcoma. This resolved completely following 1,000 r cobalt 60 radiation therapy. (B) Recheck mammography reveals complete regression of the mass originally noted in A; however, it also shows a new mass that similarly responded to subsequent cobalt radiation.

s larger than that measured on the roentgenogram.

Lymphosarcoma is radiosensitive; therefore, a therapeutic test of irradiation can provide a diagnostic test as well. Case VI is illustrative of this point.

In the differential diagnosis, the roentgenologist must consider cysts which have sharp outlines. However, cysts are generally scattered throughout both breasts, and are characteristically soft and fluctuant to palpation. Primary sarcoma is not so well margined and is clinically more firm.

Fibroadenomas, which resemble sarcomas, tend to be bosselated and are associated frequently with diffuse adenosis and coarse calcification scattered throughout both breasts. None of our cases contained the fine clumps of calcific deposit which are known to occur in intraductal and scirrhous carcinomas.

The pathologist cannot differentiate grossly between specimens of giant fibroadenoma and cystosarcoma phylloides; therefore, it is not surprising that the radiologist should experience similar difficulty.⁴



FIG. 7. Case VII. Lateral view of the breast of a forty-eight year old female revealing multiple conglomerate sharply circumscribed masses due to extensive involvement of the breast and axillae by lymphosarcoma.

Although medullary carcinomas may resemble sarcomas because they may be well defined, this type of carcinoma will frequently have some infiltrating tissue springing from the margin, an appearance which is not observed in sarcomas. And, of course, other features such as punctate calcification and distortion of the perifocal tissues due to infiltration and reaction are seen in these cancers, whereas there is only displacement of surrounding tissues in sarcomas.

SUMMARY

Sarcoma of the breast is a rare lesion. The roentgenographic appearance of sarcoma is that of a large, dense, rapidly growing, well-defined mass. It is not infiltrative and tends to resemble benign lesions such as cysts and fibroadenomata. The history of rapid growth should put the roentgenologist on guard and lead him to urge a diagnostic resection, even though the lesion may resemble a benign process on the roentgenogram.

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BREAST CANCER*

FIVE YEAR RESULTS: TWO RANDOM SERIES OF SIMPLE
MASTECTOMY WITH POSTOPERATIVE IRRADIATION
VERSUS EXTENDED RADICAL MASTECTOMYBy SIGVARD KAAE and HELGE JOHANSEN
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IN RECENT years there has been much disagreement as to the treatment of breast cancer, especially in operable cases.

After Halsted and Willy Meyer, in 1894, introduced the routine use of radical mastectomy in operable breast cancer, this was the normal method in most clinics until about twenty years ago, although many have supplemented it with preoperative and/or postoperative radiotherapy.^{8,13,14}

During the last two decades attempts to improve the therapeutic results have followed two different courses: (1) A more limited operation supplemented by heavy postoperative radiotherapy, the operation usually being simple mastectomy (McWhirter¹¹) or in the case of small tumors merely excision of the growth (Mustakallio¹²); heavy and very prolonged radiotherapy alone has also been used, without any operation (Baclesse³, Lenz¹⁰). McWhirter is the chief advocate of the systematic use of simple mastectomy with heavy postoperative irradiation to the chest wall, axilla, supraclavicular region, and internal mammary chain on the operated side. (2) An extension of the Halsted operation to include also dissection of the supraclavicular and/or internal mammary lymph nodes (Dahl-Iversen,² Urban,¹⁷ Wangenstein¹⁹).

To this day there is a divergence of opinion regarding the value of these modalities *viz.*, whether simple mastectomy with postoperative roentgen irradiation by the McWhirter method gives late results comparable to those of mastectomy with axillary dissection and whether the extended radical operations afford better results than the

ordinary radical mastectomy. The main reason why it has not so far been possible to evaluate the various forms of treatment is that the series of cases which have been compared have not been ideally matched. Results have been compared partly from different hospitals and partly from different periods of time in the same hospital. Even in the latter case, there is no guarantee that the series are comparable. In clinics where the therapeutic principle has remained the same, the therapeutic results have improved from each five year period to the next,^{4,6,15} no doubt for two reasons: (a) the patients are on the whole presenting themselves at an earlier stage of their disease and (b) the criteria of operability have been restricted.^{6,7}

In order to obtain two comparable groups, all new cases of breast cancer admitted to the Radium Centre, Copenhagen, since November, 1951 have been divided into two groups. This applies, however, only to patients domiciled in Copenhagen. On arrival, the patients were given a case number, odd numbers being assigned to Group A and even numbers to Group B. This gave two approximately equal groups. In Group A the therapeutic principle in operable cases was simple mastectomy, carried out at the Bispebjerg Hospital, Department A, with postoperative roentgen irradiation by the McWhirter¹¹ method at the Radium Centre. In Group B the therapeutic principle was extended radical mastectomy with dissection of the lymph nodes in the supraclavicular region and the second to fourth intercostal spaces by the method of Dahl-

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Iversen.^{2,16} This operation was carried out at the University Hospital, Department C, and no postoperative radiation was administered. Inoperable patients and the few operable patients who refused surgery were treated, in both groups, by radiation or hormones.

Thus, all patients were examined primarily at the Radium Centre, where the staging was carried out, and all were followed up at the Radium Centre. Staging was done in part according to the international clinical staging and in part according to Haagensen.

During the period November, 1951 to 1957, a total of 333 cases were assigned to Group A in which the treatment of operable cases was mastectomy with postoperative roentgen irradiation, while 335 were assigned to Group B, *i.e.*, extended radical mastectomy in operable cases. The therapeutic results up to December 31, 1959 were analyzed, and in all cases, excepting one, the patients were traced. The follow-up period was three years in 295 and 296 cases respectively and five years in 182 cases in each group. In other words, the time of observation is still rather short, but since no other clinics have comparable

groups of this nature, the preliminary results are probably of interest.

The age distribution in the two groups was approximately the same, 22 per cent being in the age group seventy to ninety-four years.

The total material, comprising 333 patients assigned to Group A on a basis of odd history numbers and 335 patients assigned to Group B on a basis of an even terminal digit, revealed practically identical results (Table 1). Thus, the three year survival was 67 per cent and 66 per cent respectively and the five year survival 54 per cent and 55 per cent respectively, the three year recurrence-free survival 55 per cent and 49 per cent respectively, and the five year recurrence-free survival 44 per cent and 38 per cent respectively.

Table II shows the stage distribution according to the revised classification of the Unio internationalis contra cancerum.⁵

We have classified the cases into operable and inoperable groups according to criteria similar to those of Haagensen.⁷ This classification was done preoperatively in order to be able to compare the results of simple mastectomy plus postoperative irradiation with those of extended radical mastectomy

TABLE I
TOTAL MATERIAL

		Three-Year Follow-up			Five Year Follow-up		
		No. of Cases	Survival (per cent)	Recurrence-free Survival (per cent)	No. of Cases	Survival (per cent)	Recurrence-free Survival (per cent)
All Cases	Group A	295	67	55	182	54	44
	Group B	296	66	49	182	55	38
Operable cases	Group A	259	73	62	160	61	50
	Group B	240	75	59	146	64	46
Clinical Stage I cases	Group A	147	82	73	95	71	62
	Group B	142	85	70	83	76	57
Operable minus Stage I cases	Group A	112	63	46	65	46	32
	Group B	98	61	42	63	48	32

Group A: The therapeutic principle in operable cases was simple mastectomy with postoperative roentgen irradiation by the McWhirter method.

Group B: The therapeutic principle in operable cases was extended radical mastectomy by the method of Dahl-Iversen.

TABLE II
STAGE DISTRIBUTION OF ALL CASES

	Group A	Group B
Total No.	333	335
Stage I	51%	48%
Stage II	16%	15%
Stage III	27%	28%
Stage IV	6%	9%

alone. Therefore no corrections have been made on the basis of the findings at operation. The operable groups including Stage I, Stage II and parts of Stage III account for 87 per cent Group A and 81 per cent Group B cases.

In the operable groups the three year survival (Table I, Fig. 1) was 73 per cent and 75 per cent respectively, the five year survival 61 per cent and 64 per cent respectively, the three year recurrence-free survival (Table I, Fig. 2) 62 per cent and 50 per cent respectively, and the five year recurrence-free survival 50 per cent and 46 per cent respectively.

In Stage I (Table I) the three year survival was 82 per cent and 85 per cent respectively, the five year survival 71 per cent and 76 per cent respectively, the three year recurrence-free survival 73 per cent and 70 per cent respectively, and the five year recurrence-free survival 62 per cent and 57 per cent respectively.

In the operable cases minus Stage I, i.e., Stage II and the operable part of Stage III (Table I), the three year survival was 63 per cent and 61 per cent respectively, the five year survival 46 per cent and 48 per cent respectively, the three year recurrence-free survival 46 per cent and 42 per cent respectively, and the five year recurrence-free survival 32 per cent in both groups.

Not all the patients of the operable groups received the treatment scheduled for the groups (Table III). All Group A cases were to have been treated by simple mastectomy and postoperative roentgen irradiation by the McWhirter method, which, however, was carried out in only

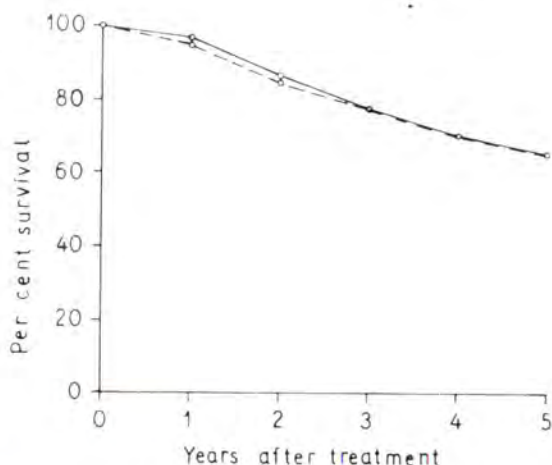


FIG. 1. Survival in operable cases.

Group A: The therapeutic principle was simple mastectomy with postoperative roentgen irradiation by the McWhirter method.

Group B: The therapeutic principle was extended radical mastectomy by the method of Dahl-Iversen.

76 per cent. No operation was performed in 12 per cent as the patients were biologically inoperable due to senility or concomitant diseases and 2 per cent refused operation. In the remaining 10 per cent the patients

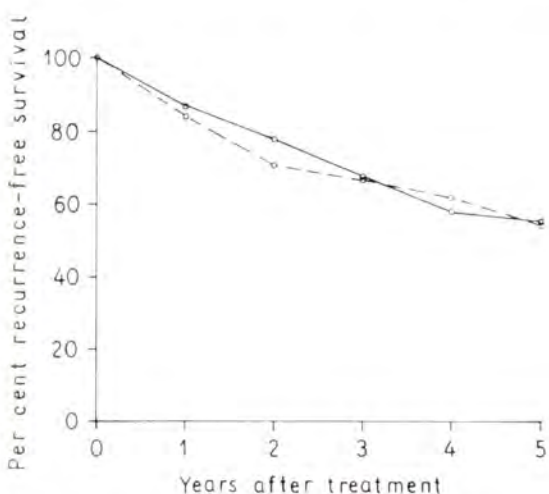


FIG. 2. Recurrence-free survival in operable cases.

Group A: The therapeutic principle was simple mastectomy with postoperative roentgen irradiation by the McWhirter method.

Group B: The therapeutic principle was extended radical mastectomy by the method of Dahl-Iversen.

TABLE III
SURVEY OF TREATMENT IN OPERABLE CASES

Group A		Group B	
Total	291	Total	271
McWhirter's method	76%	Extended radical mastectomy	76%
Biologically inoperable cases	12%	Biologically inoperable cases	13%
Refused operation	2%	Refused operation	1%
Other exceptions	10%	Other exceptions	10%

wished to be treated in other hospitals; in most cases simple mastectomy or a classic Halsted operation with postoperative irradiation was performed. These cases are included in the total series, but are excluded in comparing the end results of the McWhirter treatment with those of extended radical mastectomy.

In Group B the patients of the operable group were to have extended radical mastectomy. Seventy-six per cent were admitted to the Surgical Department C of the University Hospital to have this operation which was carried out in all except 25 cases or 12 per cent of the 206 cases. At operation 15 proved technically inoperable, 8 were in too poor condition for extended radical mastectomy, and 2 refused to have extended radical mastectomy. Instead, they had simple mastectomy, in some cases with partial excision of the lymph nodes, and postoperative roentgen irradiation. Thirteen per cent did not have operation because of biologic inoperability, *i.e.*, advanced age or concomitant diseases, and 1 per cent refused. Again, 10 per cent of the patients desired treatment in other hospitals and in most cases simple mastectomy or a classic Halsted operation with postoperative irradiation was performed. These are included in the total series, but are excluded in comparing the end results of the McWhirter treatment with those of extended radical mastectomy.

Thus the number of patients who had treatment differing from the schedule was 10 per cent in each group, and the reasons were unrelated to the stage of the cancer. The operable cases of Group A who had

simple mastectomy with postoperative roentgen irradiation by the McWhirter method, and Group B cases who had extended radical mastectomy, or less extensive surgery if they proved inoperable at operation, may be considered comparable groups without any systematic selection. There were no postoperative deaths and only one patient was untraced in the group with extended radical mastectomy.

There was no difference between the therapeutic results in these two groups (Table IV, Fig. 3 and 4). The three year survival was 78 per cent and the five year survival 66 per cent in each group, the three year recurrence-free survival 68 per cent and 67 per cent respectively, and the five year recurrence-free survival 55 per cent and 54 per cent respectively. In Stage I the three year survival was 93 per cent and 89 per cent respectively, the five year survival 74 per cent and 77 per cent respectively, the three year recurrence-free survival 79 per cent and 77 per cent respectively, and the five year recurrence-free survival 65 per cent and 63 per cent respectively. In the operable cases minus Stage I, the three year survival was 66 per cent and 62 per cent respectively, the five year survival 53 per cent and 49 per cent respectively, the three year recurrence-free survival 52 per cent and 50 per cent respectively, and the five year recurrence-free survival 38 per cent and 39 per cent respectively.

About 22 per cent of all patients were seventy years of age and over, and a large number of these elderly patients was operated upon. No correction has been made in

TABLE IV
COMPARISON OF MCWHIRTER'S METHOD AND EXTENDED RADICAL MASTECTOMY

		Three Year Follow-up			Five Year Follow-up		
		No. of Cases	Survival (per cent)	Recurrence-free Survival (per cent)	No. of Cases	Survival (per cent)	Recurrence-free Survival (per cent)
Operable cases	McWhirter's method	192	78	68	124	66	55
	Extended radical mastectomy	181	78	67	109	66	54
Clinical Stage I cases	McWhirter's method	115	86	79	77	74	65
	Extended radical mastectomy	115	87	77	68	77	63
Operable minus Stage I Cases	McWhirter's method	77	66	52	47	53	38
	Extended radical mastectomy	66	62	50	41	49	39

the analysis, not even for patients who have died without evidence of recurrence. Therefore, the results of the two therapeutic methods in the operable groups were analyzed separately for patients under seventy years of age (Table v). In this respect too, the results in the two groups were almost the same: three year survival 78 per cent and 76 per cent respectively, five year survival 68 per cent and 65 per cent respectively, three year recurrence-free survival 68 per cent and 61 per cent respec-

tively, and five year recurrence-free survival 55 per cent and 49 per cent respectively. In Stage I the three year survival was 87 per cent and 89 per cent respectively, the five year survival 77 per cent and 79 per cent respectively, the three year recurrence-free survival 80 per cent and 78 per cent respectively, and the five year recurrence-free survival 67 per cent and 66 per cent respectively. In the operable cases minus Stage I the three year survival was 65

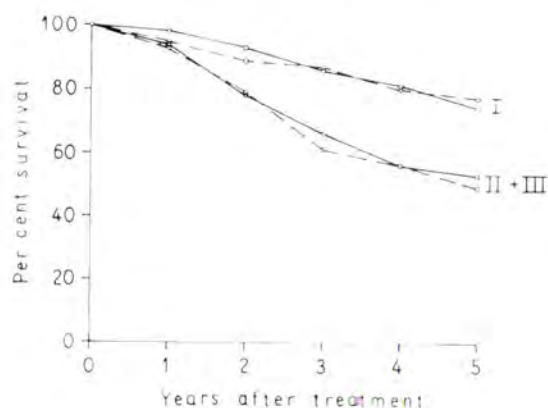


FIG. 3. Survival in operable cases.

— Treatment: Simple mastectomy with postoperative roentgen irradiation by the McWhirter method.

- - - - - Treatment: Extended radical mastectomy by the method of Dahl-Iversen.

(I) Clinical Stage I cases. (II and III) Operable cases minus Stage I cases, i.e., Stage II cases and the operable part of Stage III cases.

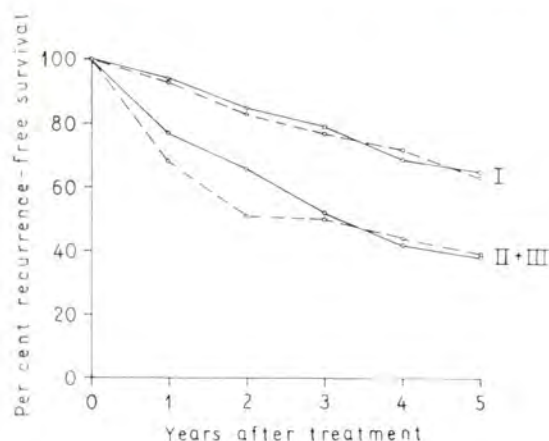


FIG. 4. Recurrence-free survival in operable cases.

— Treatment: Simple mastectomy with postoperative roentgen irradiation by the McWhirter method.

- - - - - Treatment: Extended radical mastectomy by the method of Dahl-Iversen.

(I) Clinical Stage I cases. (II and III) Operable cases minus Stage I cases, i.e., Stage II and the operable part of Stage III cases.

TABLE V
COMPARISON OF MCWHIRTER'S METHOD AND EXTENDED RADICAL MASTECTOMY
Age <70 Years

		Three Year Follow-up			Five Year Follow-up		
		No. of Cases	Survival (per cent)	Recurrence-free Survival (per cent)	No. of Cases	Survival (per cent)	Recurrence-free Survival (per cent)
Operable cases	McWhirter's method	177	78	68	111	68	55
	Extended radical mastectomy	186	76	61	113	65	49
Clinical Stage I cases	McWhirter's method	102	87	80	66	77	67
	Extended radical mastectomy	101	89	78	58	79	66
Operable minus Stage I Cases	McWhirter's method	75	65	52	45	53	38
	Extended radical mastectomy	85	60	41	55	49	31

per cent and 60 per cent respectively, the five year survival 53 per cent and 49 per cent respectively, the three year recurrence-free survival 52 per cent and 41 per cent respectively, and the five year recurrence-free survival 38 per cent and 31 per cent respectively.

The incidence of local recurrence of the chest wall, in the axilla, and in the supraclavicular region on the operated side was not higher following simple mastectomy with postoperative roentgen irradiation by the McWhirter method than following radical mastectomy (Table VI).

Thus, the preliminary comparison of simple mastectomy plus postoperative roentgen irradiation by the McWhirter method with extended radical mastectomy by Dahl-Iversen's method shows no definite difference in therapeutic results. This does not, however, justify the conclusion that the same will apply after a longer follow-up, e.g., ten years. It could be possible that simple mastectomy with postoperative irradiation might be followed by a relatively larger number of late recurrences. McWhirter's own results, however, militate against this possibility.

SUMMARY

Since November, 1951, all new patients with breast cancer from Copenhagen admitted to the Radium Centre, have been

divided into two groups. In one group the operable cases had simple mastectomy with postoperative roentgen irradiation by the McWhirter method. In the other group the operable cases had extended radical mastectomy by the method of Dahl-Iversen. The preliminary therapeutic results show no definite difference between the results of the two methods.

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TABLE VI
LOCAL AND REGIONAL RECURRENCE

Five Year Results

Group A: McWhirter's method: 124 patients
Group B: Extended radical mastectomy: 109 patients

	Recurrence of Chest Wall (per cent)	Recurrence in Axilla (per cent)	Recurrence in Supraclavicular Region (per cent)
Group A	7	8	2
Group B	10	13	3

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THE MEASUREMENT OF BUILD-UP ON CURVED SURFACES EXPOSED TO Co^{60} AND Cs^{137} BEAMS*

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THERE have been a number of investigations of skin reactions following supervoltage irradiation. A recent paper by Liegner and Michaud⁵ includes most of the pertinent references on this subject.

It is well known that the dose variation in the first few millimeters of depth depends upon the electron contamination in the beam which, in turn, depends upon the type of collimator used to control the radiation.³ Since the dose variation in the superficial layers can seldom be predicted accurately from one machine to another, it is usually necessary to perform physical measurements of build-up in conjunction with clinical investigations of the skin reactions.¹ Most build-up studies in the past have involved the use of radiation directed normal to the skin surface and only a little information² is available concerning the dose build-up when the beam strikes the skin almost tangentially, that is, at angles of incidence close to 90° . Dose build-up under conditions of tangential irradiation will be discussed in this paper.

One clinical condition involving tangential irradiation is that encountered when the chest wall is irradiated following removal of the breast. It is usual to treat the chest wall using two opposing pairs of fields. The angle of incidence of the beam varies from point to point over the cylindrical-like chest wall approaching 90° (tangential) along a line midway between the two fields. Under these circumstances it is quite impossible to estimate the dose distribution in the superficial layers from published data since most of them apply to normal incidence. In addition, there is no general agreement as to whether a bolus should or should not be used when a tan-

gential technique is employed for the treatment of the chest wall with Co^{60} or Cs^{137} radiation.

To investigate the relative advantages of bolus versus no bolus, extensive measurements have been made of the dose distribution in the superficial layers for single and parallel opposing fields applied to a phantom shaped like a chest wall. Our findings indicate that for Co^{60} optimum distributions are obtained using full bolus, while for Cs^{137} bolus should only be used for a half of the treatment series. A better distribution can be obtained using Co^{60} in this way than can be achieved with Cs^{137} .

EXPERIMENTAL METHOD

All dosimetry was performed using Adox KB 14, a single emulsion photographic film with an emulsion thickness of approximately $8\ \mu$ and a total thickness of $125\ \mu$. A number of strips of film were exposed on a phantom as described below. After exposure, these strips were loaded into standard 35 mm. developer reels and were developed together in a large tank. Development was in D-76 for ten minutes at 68°F ., with agitation every ten seconds.

The phantom, on which the films were exposed, was made by pouring paraffin wax into a plywood shell (Fig. 1). A central groove 37 mm. wide and 5 mm. deep along the curved surface allowed a number of strips of film to be exposed simultaneously. For some experiments, lucite strips were used to separate the layers of films when it was anticipated that the dosage gradient would be small. The film had to be isolated from both the lucite strips and the paraffin wax to prevent blackening by Cerenkov radiation.

The film was exposed to the beam in a

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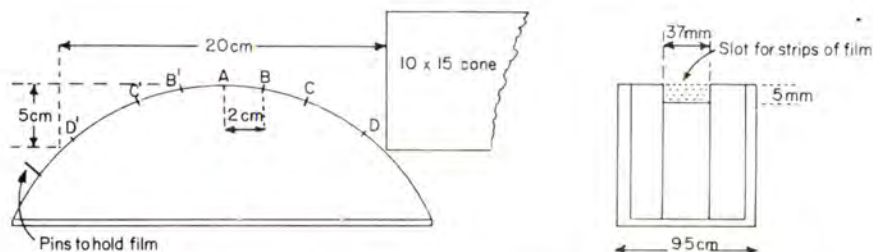


FIG. 1. Paraffin wax phantom. Point A is the apex of the curved surface; Points B and B', C and C', D and D' are 2, 4 and 8 cm., respectively, from the midline.

darkened room so that no light could reach it. The irradiation was given from one side only for a measured period of time using a 10×15 cm. cone. Films for dose density calibration were exposed normal to the center of the beam.

The accuracy of film dosimetry for this work was checked in the following ways:

- (a) To check the response of the film for various angles of incidence, a depth dose distribution was obtained as follows: A single film held at right angles to the surface of a water phantom was exposed to a vertical beam of radiation. Then a series of calibration films, placed at the equilibrium depth, were exposed for a series of times with the beam normal to the surface. The densities of these calibration films were plotted as a function of time (and hence dose) and were used to determine the depth dose from the single film. The depth dose agreed with published data for Co^{60} indicating that the response of film did not depend upon the angle of incidence of the radiation.
- (b) By using a series of films packed together with thin spacers, the dose distribution for the first few millimeters was determined for Cs^{137} and is shown in Figure 4. This dose build-up curve was in agreement with measurements made on the same cesium unit using a thin walled ionization chamber,⁴ thus indicating that film dosimetry is satisfactory for the build-up region.

RESULTS

Cobalt 60. Figure 2 shows the dose distribution in the superficial layers of the curved phantom at the entrance and exit sides of the phantom. The dosage is plotted as a function of depths measured normally from the surface under the points A, B, C, D and B', C', D' of Figure 1. Doses are expressed as a percentage of the air dose with full build-up measured at the end of the treatment cone. Depths are given in millimeters for unit density material. Depth scales run from right to left for the exit measurements and from left to right for the entrance measurements.

Curve A represents the build-up under the apex of the chest wall at a place where the field is exactly tangential. The maximum dose is reached at approximately 1.5

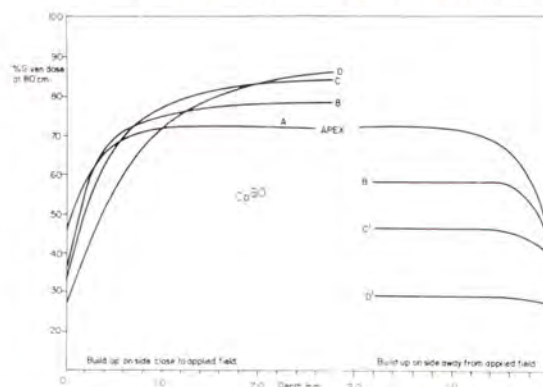


FIG. 2. Measured dose distribution as a function of depth for both the entrance and exit portion of the field using a Co^{60} field (10×15 cm.) directed onto the phantom shown in Figure 1. The letters refer to the positions shown in Figure 1.

mm. depth and is 73 per cent of the given air dose at 80 cm. The apex of the phantom is 10 cm. from the end of the treatment cone; hence, not considering scatter, the dose should be $(80/90)^2 100 = 79$ per cent. However, there are several factors which lower the dose below the calculated one. The axial ray from the machine actually has to penetrate about 1.5 cm. of tissue to reach the point 1.5 mm. below A, so some absorption will take place tending to lower the dose. Scatter from points below the apex will tend to raise the dose slightly. Evidently this latter effect is less than the former.

At B, the beam enters more nearly at right angles and the point of equilibrium is reached at a greater depth, approximately 2.6 mm. The maximum is lower than the calculated value for the same reasons. Point D receives radiation almost normal to the surface but, because it is near the edge of the field, the dose is only 90 per cent of the maximum value. Similar curves are obtained for points B', C' and D'.

If the curves for B and B', etc., are added together, the dosage distribution obtained is identical to that which would result from two parallel opposing Co^{60} beams directed on the phantom with a separation of 20 cm. The results are shown in Figure 3, where the dose at various depths is shown as a function of distance from the midline. For any one depth the dose varies by about 50 per cent over the curved surface, with the peak dose at the apex. The dose variation with depth at any one position varies by an even larger factor.

Cesium 137. Figure 4 shows the dose distribution for Cs^{137} , corresponding to Figure 2 for Co^{60} . As with Co^{60} , the maximum value under the apex of the curved surface (54 per cent) is less than the value calculated by the inverse square law $(35/45)^2 = 60$ per cent. For tangential irradiation (Point A) the point of electronic equilibrium is not at the surface, but at a depth of 0.65 mm.

Note that, in this case, the surface dose at D is greater than at A, while with Co^{60}

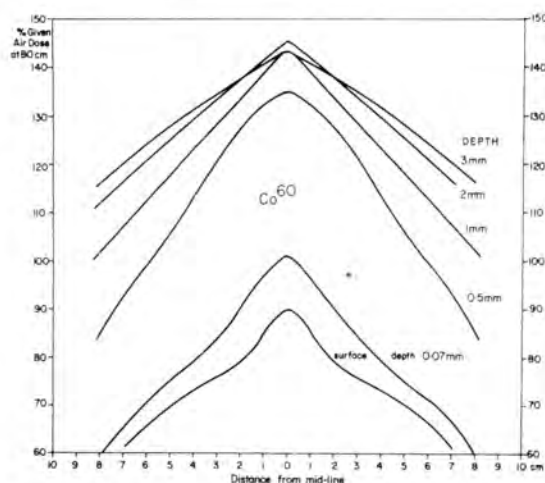


FIG. 3. Resultant dose at various depths for two Co^{60} fields (15×10 cm.) applied to the curved chest wall with a separation of 20 cm.

the reverse was true. This is due to the differences in source to skin distance for the two machines.

The addition of the doses received at B and B', etc., gives the dosage distribution which would be obtained from two parallel opposing fields separated by 20 cm. The resultant distributions are shown in Figure 5.

DISCUSSION

The physical aim in irradiation of the chest wall is to deliver as homogeneous a

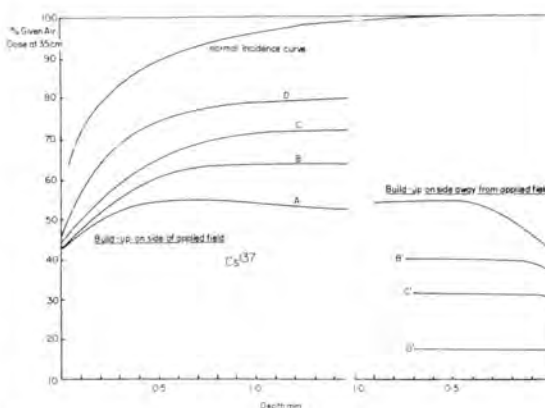


FIG. 4. Measured dose distribution as a function of depth for both the entrance and exit portion of the field using a Cs^{137} (10×15 cm.) field directed onto the phantom shown in Figure 1. The letters refer to the positions shown in Figure 1.

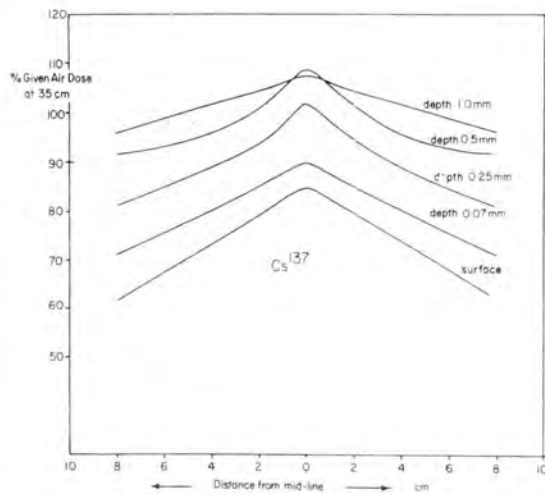


FIG. 5. Resultant dose at various depths for two Cs^{137} (15×10 cm.) fields applied to the curved chest wall with a separation of 20 cm.

dose as possible throughout the irradiated tissue. It can be seen from the above results that, when bolus is not used with Co^{60} , the superficial layers of the skin receive much less radiation than the tissues a few millimeters deep. If we assume the basal layer of the epidermis to be at a depth of 0.07 mm., then the dose to these cells with Co^{60} is less than 70 per cent of the maximum dose which is attained at a depth of 2.0 mm. In addition, the variation in dosage over the chest wall is some 40 per cent, which is much larger than the 10 per cent variation acceptable to many radiotherapists.

Figure 6 shows the resultant distribution through the tissue for any depth if full bolus is used with Co^{60} . This is a calculated curve based on published depth dose data. The dose variation throughout the tissue is small and can be readily calculated for any field separation. However, the skin sparing effect of Co^{60} radiation is lost. If one attempts to lessen the skin reaction by giving the first half of a series of treatments without bolus and the second half with bolus, the spread between surface dose and depth dose differs by more than 10 per cent, as illustrated in Figure 6.

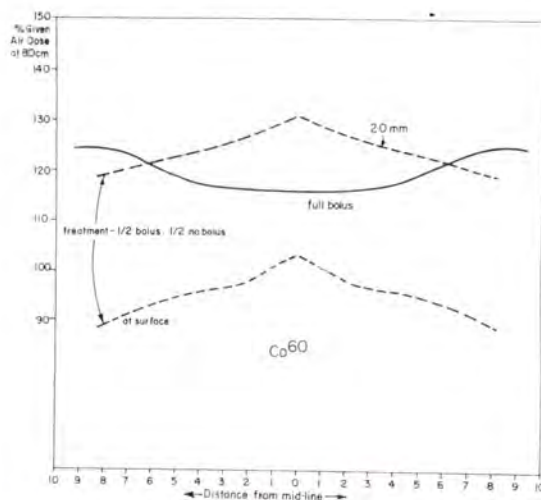


FIG. 6. Dose distribution using full bolus and dose distribution when bolus is used for half of the treatments. Irradiation by two (10×15 cm.) Co^{60} fields separated by 20 cm, treating the curved chest wall.

Figure 7 shows similar results for Cs^{137} . The use of a full bolus does not give a homogeneous dose across the curved surface, although the spread is not quite as large as when no bolus is used (Fig. 5). To obtain a homogeneous dose at any one depth, it becomes necessary to carry out half the treatments with bolus and the other half without, as demonstrated in Figure 7. To obtain this homogeneity

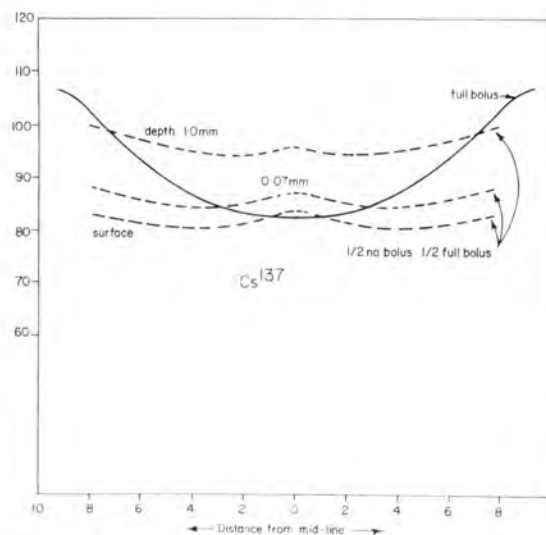


FIG. 7. Dose at various depths using a partial or full bolus (Cs^{137} , parallel opposing fields).

with position one loses some homogeneity with depth. Now the spread of dosage from the surface to a depth of 1.0 mm. is greater than 10 per cent but this is much less than with the other two possible treatment methods.

The phantom used was solid and no effort was made to take into account the effect in lung tissue. With Co^{60} and Cs^{137} side scatter is unimportant, so that the dose as measured at A A', B B', C C' in our phantom should be very nearly the same as the dose measured in a patient. In the average patient the line D D' might pass through a little lung tissue and the dose at these points might be higher than measured in our experiments.

SUMMARY

In the irradiation of the chest wall following removal of the breast, it is usual to use tangential fields. However, there has been no agreement as to whether bolus should or should not be employed. Under conditions of full bolus, the dose may be estimated readily from isodose curves, but with no bolus little information concerning the dose in the superficial layers of the skin has been available. Extensive measurements on a cylindrical phantom using thin

emulsion films exposed to both Co^{60} and Cs^{137} radiation have been made. This study shows that with Co^{60} a better distribution of radiation is obtained when bolus is used. For Cs^{137} the most satisfactory distribution is obtained using bolus for half the series of treatments and no bolus for the rest.

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ACTINOMYCIN D AND RADIATION THERAPY*

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SINCE we are in an era of combined cancer therapies, the radiation therapist should be acquainted with the combination of actinomycin D, an antibiotic, and radiation therapy. Various practitioners will certainly confront the radiotherapist with suggestions for its use. One should possess a basic knowledge of its properties, complications, potentialities and limitations before adequate recommendation for use or rejection can be given. In addition to practical criteria for using the drug, comments will be presented resulting from recent tissue culture study.

HISTORICAL DEVELOPMENT

A common query is—what is actinomycin D? In 1940, Waksman and Woodruff²⁹ derived actinomycin, a red pigment, using an ether extract of a culture broth, from a soil organism, *Actinomyces antibioticus*. In modern classification the name has been changed to *Streptomyces antibioticus*. Subsequently, actinomycin has been shown to be a common antibiotic product of the soil *Streptomyces*. During the period 1941 to 1958, at least 11 different species names have been given to the producing cultures. Waksman *et al.*²⁸ have classified the culture actinomycin producing strains into three basic types: (a) chromogenic with straight sporophores, (b) nonchromogenic with straight sporophores, and (c) nonchromogenic with coiled sporophores. In 1954, Manaker *et al.*¹³ reported the actinomycin D complex from *Streptomyces parvullus*. This culture is a nonchromogen with spiral sporophores.

The complexes derived from the various cultures had differences in their chemical properties and these were designated by a letter: *viz.*, A, B, C, D, F, J, I, M, X and Z. The culture method, age of culture, and the nitrogen source of the culture medium

used are important factors influencing the biosynthesis.

Preparations of actinomycin are a mixture of chemical entities in varying proportions. Waksman and Tishler³¹ gave the chemical nature as a polycyclic nitrogen compound. The variations are limited to substitutions among the amino acids of the peptide chains. A distinct pure chemical actinomycin has been designated by Waksman *et al.* by Roman numerals I to VII. Actinomycin D is composed of actinomycin IV. In 1957, a chemical structure was given to actinomycin D by Bullock and Johnson¹ (Fig. 1). For a detailed clarification of the nomenclature of the actinomycins, reference should be made to an article by Waksman and co-workers.³⁰ An excellent monograph on the actinomycins was published in 1960.²⁷

The antibiotic activity of the actinomycins led to their discovery but their extreme toxicity prevented their general use against infectious agents. Because of this toxicity, investigators turned their studies to the cytotoxic action of the actinomycins on various tumors and tissues. Earlier investigators had shown detectable levels of inhibition upon the growth of sarcoma 180 in the mouse.^{18,25} Recently, Mihich *et al.*¹⁴ compared the cytotoxic activity when sarcoma 180 was transplanted from treated donor mice into untreated recipient mice. Of the eight drugs studied, actinomycin D was one of the two that proved to be the best tumor inhibitor.¹⁴ In 1956 Eagle and Foley⁵ reported the cytotoxic activity of actinomycin D *in vitro* in 6 established cell lines derived from human or mouse normal and neoplastic tissue. Smith *et al.*²³ reported on the cytotoxicity of a group of antibiotics, chemicals and solvents on a tissue culture KB strain of epidermoid carcinoma cells. Actinomycin D was the

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most cytotoxic agent tested ($ID_{50} = 6 \times 10^{-5} \mu\text{g./ml.}$). In none of the early animal or tissue culture work was the drug combined with irradiation.

In 1957, Hackman and Schmidt-Kastner,¹⁰ while noting the suppression of the growth of Ehrlich carcinoma, commented on the cytostatic effect of the lymphatic system. Earlier, clinical trials were carried out with actinomycin C (sarnamycin) in Hodgkin's disease.^{19,21} The general conclusion was that the drug caused a transient objective effect in some cases. Farber *et al.*,^{6,7,8} after demonstrating inhibition of tumor growth in certain mouse and rat neoplasms by actinomycin D, conducted clinical studies that showed beneficial responses in Wilms' tumor, rhabdomyosarcomas, Ewing's sarcoma and Hodgkin's sarcoma. Tan *et al.*²⁶ reported on 111 cases of children with metastatic cancer. Their conclusion was that a slight but definite effect was present in producing regression of tumors. The best results were in the

Wilms' tumor and lymphoma groups. Watne and his associates³² treated 132 adult patients with advanced malignancies. Using actinomycin D alone, they noted temporary objective regression of tumor masses in 22 of 132 patients.

THE SKIN, RADIATION THERAPY, AND ACTINOMYCIN D

Interest in combined actinomycin D and radiation treatment developed when the drug was given to some of the patients receiving radiation therapy. An increase in skin effect was noted as compared with the usual dose of radiation, and previous sites of irradiation were reactivated if the interval between radiation treatment and a subsequent course of the drug was not too long. Thus, the concept of radiation effects being enhanced or potentiated by actinomycin D was emphasized by D'Angio *et al.*⁴ from their observations on rats and humans. Tan and her group²⁶ noted increased radiation response in 18 of 28 patients who had Wilms' tumor or neuroblastoma.

The author has been able to demonstrate the increased skin effect of radiation induced by actinomycin D on Sprague Dawley rats weighing approximately 0.25 kg. each. The backs of the rats were irradiated by means of an electron beam from a 700 kv., G. E. resonance generator, $1.3 \mu\text{a}$ at 2 feet from the window with a dose of approximately 3,000 rads being

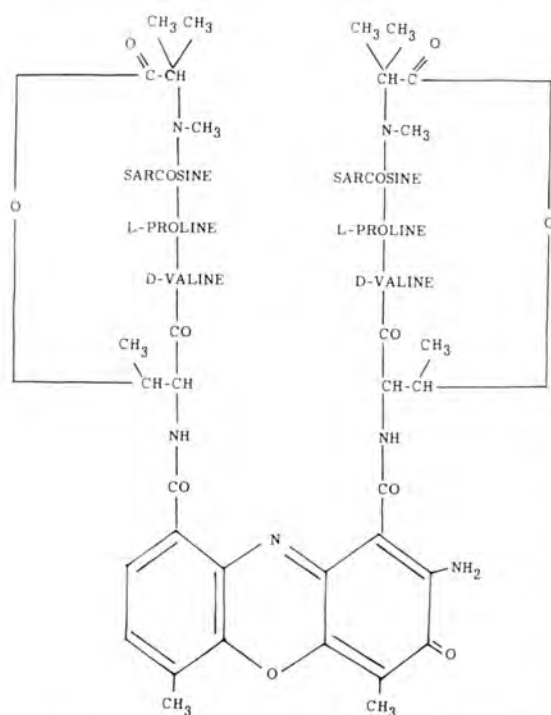


FIG. 1. Chemical structure given to actinomycin D by Bullock and Johnson.¹



FIG. 2. Fourteenth day after rat received electron beam irradiation and saline intraperitoneally. Control animal.



FIG. 3. Fourteenth day after rat received electron beam irradiation and actinomycin D intraperitoneally.

given. Figure 2 shows the skin changes present on the fourteenth day after irradiation in the control animals which received only saline injections intraperitoneally. Figure 3 is a photograph of one of the animals, also on the fourteenth day, which received 12.5 μ g. of actinomycin D the day prior to irradiation intraperitoneally, and the same dose two hours before and again twenty-four hours after irradiation, for a total of 37.5 μ g. per 0.25 kg. rat in three days. By comparing the rats one can easily note the more extensive, uniformly accelerated skin reaction in the drug treated animal. This result was achieved in our third trial of the experiment. During the first experiment the drug dose was too high and the animals died before the skin changes were optimal. The second experiment entailed administering the drug on days following irradiation and we experienced difficulty in demonstrating a difference between the groups. These errors have some clinical applications, as will be mentioned later.

When first using the drug, the radiotherapist may experience some disappointment or surprise over the skin changes that occur. In our clinical case material with over 50 courses of actinomycin D administration, we did not at all times see a marked enhancement of the erythema of the treated skin. This discrepancy between findings in humans and animals and the reports in the literature caused a skin testing of pa-



FIG. 4. Patient undergoing skin test of irradiation to study the effect of added actinomycin D.

tients to be done. It was hoped that it could be determined which patient would respond or whether a time interval was important. Figure 4 shows a patient receiving a skin test dose. Three vertical skin portals were used, 3 cm. in diameter. The superior one received 700 r, the middle one 300 r and the lower one 500 r. The radiation used was 100 kv., half value layer 1.0 mm. Al at 20 cm. distance. There were 24 patients who received such testing prior to the intravenous administration of actinomycin D and again during the course of the drug therapy. Figure 5 demonstrates the findings in a typical patient. On the right side one can see the test that was done one week before any drug was administered. On the left is the skin test on the fifth day of the



FIG. 5. The left side shows the effect of the drug causing a near uniform response for the range of radiation doses given. The right side done before the drug administration shows only a gradation effect. See text.

course of actinomycin D therapy. The left shows all portals, even the one to which 300 r was delivered, being equally activated. The right side is being reactivated by the drug, but, since the test was done earlier when there was no influence of the drug, only a gradation of effect is noted. Figure 6 shows the thigh of a child who had Wilms' tumor and who was treated with combined actinomycin D and radiation. Again the severe reaction of all portals to the levels of vesiculation and early desquamation are seen. This result cannot be obtained with irradiation alone even in the area to which 700 r is delivered.

Figure 7 shows the reactivation phenomenon that can occur in a previously irradiated skin field when actinomycin D is given after a reasonable interval and with effective dosage. The child had a massive recurrence of a mesonephroma in the pelvis following two surgical procedures. Six and three months previously, she received courses of actinomycin D and irradiation. The usual erythema for each course of 2,000 rads given to the skin was noted. A temporary clinical regression was obtained, but, when the left kidney became obstructed, it was decided to give additional actinomycin D and to irradiate the left pelvis, using a skin portal superior to the one previously used. However, after only 550 rads to this posterior portal in two weeks, there was not only mild erythema, but the older lower



FIG. 6. Skin test of child's thigh. Received combined drug and radiation therapy for Wilms' tumor of left kidney. Early vesiculation and desquamation in all portals were noted from doses of 700 r, 300 r and 500 r, left to right, respectively.



FIG. 7. Skin changes resulting from repeated courses of actinomycin D and irradiation. Three year old female child who had a massive recurrence of a mesonephroma following 2 surgical procedures. A mild reaction can be seen in a superior portal, but the marked change is the reactivation of treatment fields used 3 to 6 months previously.

midline treated fields showed excessive erythema and early vesiculation, more than at any earlier treatment period.

As there has been some variability in the degree and frequency of these skin changes, some of the factors necessary to produce them can be mentioned. Since actinomycin D is a toxic drug, dosage has to be sufficient in order to observe signs of this clinically, of which the skin change is one. With low dosage one is less likely to see these effects. Our adult patients have regularly shown the skin effects while receiving 1 mg. a day for five days. A four



FIG. 8. Abdomen of a four and one-half year old female who received 1,000 rads to the left upper quadrant by a 10×15 cm. portal and actinomycin D therapy. Increased erythematous response is present, but the drug and adhesive dressings caused areas of skin outside the treated field to become denuded.

and one-half year old white female with Wilms' tumor had severe skin reaction and other signs of toxicity after receiving 225 μ g. per day for five days (one course). Other pediatric patients have had 2 courses and have failed to show any striking skin effects. Perhaps individual tolerance or hypersensitivity to the drug may be a contributing factor. It is also probably important that a definite time interval between the administration of the drug and the subsequent irradiation be observed. Skin changes are more readily produced if actinomycin D is given intravenously two to four hours preceding the irradiation. Ranniger and Griem¹⁷ advocated this treatment schedule in a report in which they described experimental animal results. Changes are less likely to occur if the interval is too long since the drug concen-

tration is reduced in the body. If given some time after the irradiation, the effect of the drug is lost. Lastly, as mentioned earlier, the actinomycins are a chemical mixture and variations may be produced in manufacturing the drug. Freshness of the actinomycin D should also be ensured and sunlight should be avoided when the material is stored.

It might be of benefit to comment on other aspects of skin involvement that can occur while using combined actinomycin D with irradiation. Figure 8 shows the abdomen of a child who had immediate post-operative irradiation for a Wilms' tumor of the left upper quadrant only, through a 10×15 cm. field. She received 1,000 rads and an unexpected moderate erythema developed. The denuded areas of skin, re-



FIG. 9. Same child as in Figure 8, 5 days later. Note areas of reaction from adhesive dressing and actinomycin D on abdomen and left arm. Radiation was given only to a 10×15 cm. left upper quadrant field.

sulting from the adhesive bandages, were not in the treated field. Figure 9 shows the same child five days later, with extensive changes over the left mid-arm from adhesive bandages which were used to maintain intravenous fluids. The early radiation skin changes can be minor compared with the reaction to the adhesive bandages amplified by a drug effect. We advise that no adhesive dressings be used if a child is on actinomycin D therapy. Another side effect that can occur is a mild stomatitis (Fig. 10). This was seen in 20 per cent of our cases. When giving the drug intravenously, it should be diluted sufficiently and extravasation into the surrounding tissues must be avoided. In only 1 of our cases did this happen and a moderately severe induration of the tissues resulted (Fig. 11). This reaction quickly subsided and has left no sequela. In 3 of our patients there was a rather severe alopecia observed (Fig. 12). The alopecia was reversible with rapid restoration to normal (Fig. 13). The patient shown in Figures 8, 9, and 14 has been seen over a year and a half now and shows no evidence of any late potentiation effect.

It must be mentioned that these skin



FIG. 10. Two year old male child, who received actinomycin D and radiation therapy for incompletely removed Wilms' tumor, demonstrating stomatitis from the drug.



FIG. 11. The left antecubital fossa of a child in which some of the drug extravasated. These changes were reversible and no sequela resulted.



FIG. 12. Severe alopecia produced by actinomycin D in a child with Wilms' tumor (same patient as in Figures 8 and 9) one month after course of the drug. She received a total of 1.2 mg. over 5 days.



FIG. 13. Same child as in Figure 12, with full restoration of hair growth. Photograph was taken 6 months after drug therapy.

changes are the most spectacular complications that occur with the use of actinomycin D. However, the most frequent side effects are nausea and vomiting which have occurred in over 90 per cent of our patients. Antiemetic drugs give mild relief as a rule. Next in frequency is a depression of the white blood cell count. At least 40 per cent of the patients showed a leukopenia. The average low figure was about 3,000, and one child had a count of 1,100, but he was receiving large field therapy for metastatic lung disease. The leukopenic changes proved to be reversible in our experience. The usual fields used did not require us to lower our total radiation dosages significantly, but only occasionally to modify our dose rate when the patient was on actinomycin D and marked skin changes were present.

THE ADDITIVE EFFECT OF ROENTGEN RAYS AND ACTINOMYCIN D

Since there seemed to be a universal effect on the skin outside the treatment field, the thought occurred that perhaps the skin was a specific end target for the drug. Perhaps potentiation of roentgen ray effects by the drug was only additive. Since there were only a few studies of combined radiation and drug *in vitro* therapy, a tissue culture experiment was carried out.

Previously Cobb and Walker³ showed in tissue cultures that the hela cell was least affected by the drug alone. Chan and Liebner² reported their results with combined drug and radiation therapy. Figure 15 shows a hela cell culture (an epidermoid carcinoma of human cervix) after exposure to 200 r. Figure 16 is the hela cell culture after administration of actinomycin D,



FIG. 14. Abdomen of child shown in Figure 8 and 9, demonstrating full recovery and no sequelae. Healing was prompt and within the month, but photograph was made 6 months after drug therapy.

0.001 mg. per ml. Compare these changes to those of combined drug and radiation therapy (Fig. 17). By the seventh day regenerated cells can be seen (Fig. 18).

Table I is a brief summary of the protein determinations as observed in our experiment.^{15,24} The greatest inhibition of protein synthesis was noted twenty-four hours after irradiation, with moderate recovery manifested at seventy-two hours. When compared with the controls, groups treated by actinomycin D or radiation alone gave values 74 to 89 per cent of normal. The combined therapy of drug and radiation gave 50 to 58 per cent of normal protein values, thus producing the greatest inhibition of protein synthesis. It is the author's opinion that these results are more additive than potentiative in nature. Schoeniger *et al.*²⁰ have also recently reported that the concept of potentiation could not be substantiated in their tissue culture and ani-

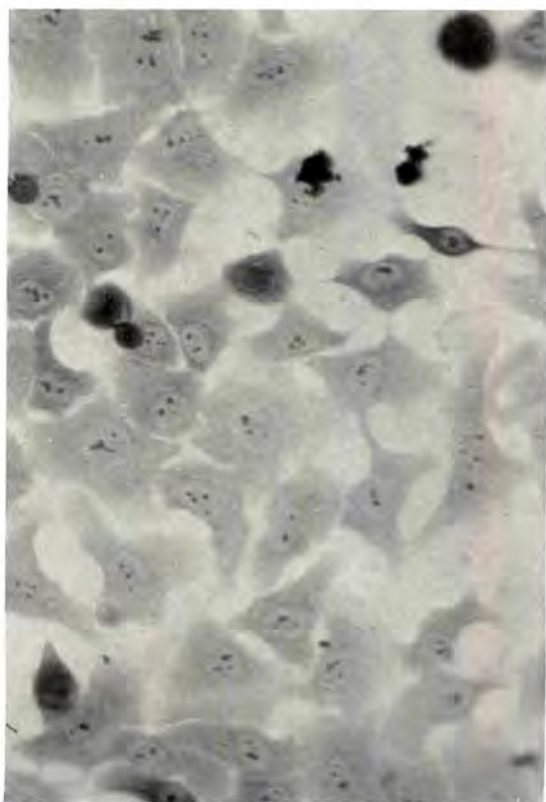


FIG. 15. HeLa cell culture 3 days after exposure to electron beam or 240 kv. (200 r).

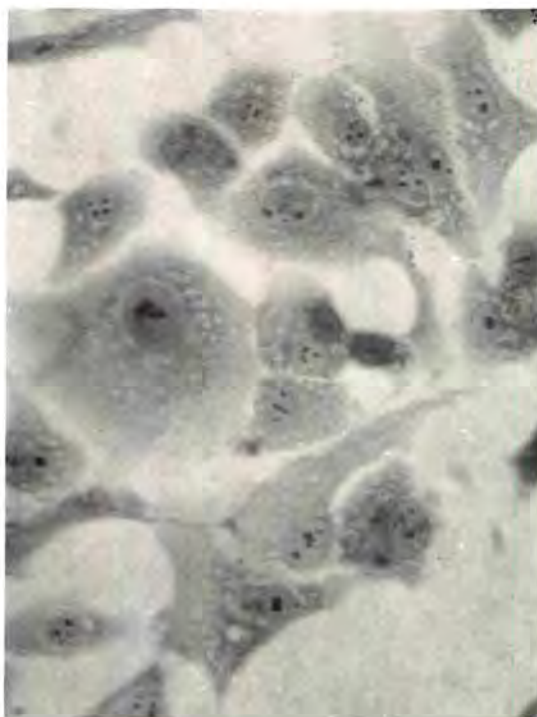


FIG. 16. HeLa cell culture 3 days after actinomycin D therapy, 0.001 mg. per ml.

mal experiments. However, Maddock *et al.*¹² have concluded from their experiments with combined actinomycin D and radiation therapy of Ridgeway osteogenic sarcoma in mice that the results were much more than additive when compared to the control group or the groups receiving actinomycin D or irradiation alone.

As a result of the effect of combined irradiation and actinomycin D on the HeLa cell *in vitro*, a small clinical pilot study has been instituted in Stage III carcinoma of the cervix cases. Perhaps more additive effects can be obtained in the parametrial regions, if technical and toxic difficulties are not too great.

The mechanism of the action of actinomycin D has been studied with the use of specific microbiologic bioassay systems.^{9,22} Foley's results indicate that the drug inhibited pantothenate utilization and suggested an interference with the synthesis and/or biologic activity of co-enzyme A. Cobb and Walker³ commented on the re-



FIG. 17. Hela cell culture 3 days after exposure to combined irradiation and actinomycin D therapy.

duction of nucleolar size in drug treated cells and stated that these changes may be explained by actinomycin D acting as a metabolic inhibitor, producing a catabolic state. Animal experiments on the toxicity of the drug have shown that the spleen, lymphoid tissue, and the intestinal epithelium are the most sensitive sites of damage.¹⁶ Thus, there is a resemblance to ionizing radiations and nitrogen mustards.

Actinomycin D as a cancerocidal agent is somewhat limited by its toxicity. A preliminary summary of our material is being reported by Liebner, Kirkpatrick and Rosenthal.¹¹ Some improvement was noted in the cases of undifferentiated sarcoma, Hodgkin's sarcoma, the mesonephroma and Ewing's tumor. This was followed, however, by secondary resurgence and growth. The cases of Wilms' tumor which were treated by nephrectomy, then radiation and actinomycin D therapy, beginning

seventy-two hours to seven days following surgery are well nearly two years after treatment. To illustrate several features, a brief summary is given of a case of rhabdomyosarcoma of the neck in a seven year old male.

ILLUSTRATIVE CASE

P.S., a seven year old white male, was first seen on August 1, 1960 with a large mass in the left side of the neck extending to the midline (Fig. 19). A tracheotomy tube was present and a laryngectomy scar was noted. The past history disclosed that he had had these surgical procedures in the early fall of 1959. Pathologic study revealed a tissue diagnosis of rhabdomyosarcoma originating from the larynx. Biopsy of the recurrent large mass was also interpreted as rhabdomyosarcoma. The patient received actinomycin D, 0.2 mg. per day for five days, and this course was again repeated two weeks later. The drug was given intra-

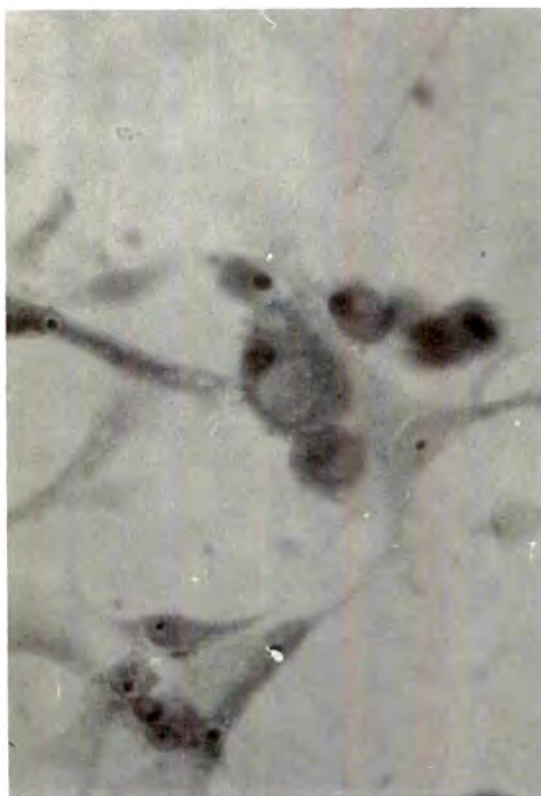


FIG. 18. Hela cell culture 7 days after combined irradiation and actinomycin D therapy, demonstrating regenerated clones of cells.

venously two hours before irradiation. He received electron beam therapy (21 mev.) through a single oblique portal 7×10 cm. from August 3 to September 30, 1960. A total of 7,800 electron beam units was given in 36 treatments. After receiving the first course of the drug and 1,000 units of radiation in the first week of therapy, the mass had disappeared and there was a moderate erythema (Fig. 20). During the following two weeks, although radiation was being given, the erythema subsided, only to return the following week when the drug was given again. To date, the child has been free of any recurrence and his general condition is excellent. (Nov., 1961)

SUMMARY AND CONCLUSION

Actinomycin D is a toxic drug and it can cause a variety of ectodermal and mucosal reactions. Since the skin of the irradiated field has shown increased erythema, investigators suggest that potentiation of the radiation effects by the drug is respon-

TABLE I
IN VITRO EFFECTS OF COMBINED RADIATION
AND ACTINOMYCIN D
Results of three experiments on total protein
determinations

	$\mu\text{g./ml.}$		
	Experi- ment 1 72 hr.	Experi- ment 2 24 hr.	Experi- ment 3 72 hr.
Controls	461	303	494
Electron beam, 200 r	446	187.5	463
240 kv., 200 r	578.6	272.5	513
Actinomycin D	434	223.5	438
Actinomycin D and electron beam, 200 r	465	177.5	499
Actinomycin D and 240 kv., 200 r	504.3	151.5	441

sible. However, one can observe excessive skin manifestations from adhesive dressing, trauma and extravasation of actinomycin D. These clinical observations and tissue



FIG. 19. Massive recurrence of rhabdomyosarcoma of larynx in a 7 year old white male. One year previously, he had a total laryngectomy for an early lesion.



FIG. 20. Marked response to combined actinomycin D and electron beam therapy. Compare with Figure 19. See text.

culture studies have prompted us to believe that the responses are additive.

In regard to the clinical use of the drug, it is advocated that the dosage be sufficient to produce some signs of toxicity and one doubts if any benefit will be obtained on lesser dosage schedules. If the drug is to be used in conjunction with radiation therapy, it is advisable that it be administered two to four hours before irradiation. From our tissue culture and protein determinations, it would seem best to give the drug every other day, trying to extend the administration as long as possible during the course of the radiation therapy.

By using the drug alone, only temporary regression can be obtained. At present, there is nothing to indicate that total radiation dosages should be lowered. At times, the dose rate of radiation may have to be reduced temporarily during episodes of skin reactions or mild neutropenia if large fields are used. The toxic reactions have all been reversible with no evidence of late sequelae. The drug should also be administered prophylactically for it is difficult to be sure that all the neoplastic cells are in the irradiated field.

Childhood tumors have received the greatest interest, but a small pilot study is being made in cases of Stage III carcinoma of the cervix.

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Actinomycin D was supplied by Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania. Appreciation is due Dr. Sol R. Rosenthal for the use of his animals and for the technical help of Mr. Alvin Goodwin and Mr. Ralph Levine. Dr. Paul Chan was responsible for the technical help in the tissue culture study, and Mr. John Megley of Abbott Laboratories aided in the protein determinations. Drs. H. Sanford and W. Mengert, Heads of the Departments of Pediatrics and Gynecology respectively, were cooperative in the clinical study. Appreciation is due Dr. R. A. Harvey for his help in the preparation of the manuscript.

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CLINICAL AND BIOLOGIC STUDIES OF ACTINOMYCIN D AND ROENTGEN IRRADIATION*

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ACTINOMYCIN D is an antibiotic which has a carcinolytic effect on certain tumors in laboratory animals and in humans.^{6-8,11,15-21} An additional remarkable property is its ability to enhance the effects of roentgen irradiation in a diversity of biologic systems.

Gross and microscopic radiation reactions in the skin of normal mice appear earlier and are more pronounced when animals receiving actinomycin D and roentgen irradiation are compared to others receiving roentgen therapy alone.^{4,13} Augmentation of radiation effects has also been demonstrated in transplantable animal tumors.¹⁴ In a series of such experiments, mice bearing the Ridgeway osteogenic sarcoma showed a better response to combined treatment than did those receiving either modality alone; tumor regression was more prolonged and survival time increased in the combined treatment group.¹² Therapeutic effects were the same when intervals ranging from ten minutes to twenty-four hours separated the administration of actinomycin D and roentgen irradiation.⁵ Augmented responses have also been demonstrated by Bases¹ and by Chan and Liebner² using tissue culture techniques.

Radiation effects in normal human skin and mucous membranes also may be potentiated by actinomycin D.^{3,15,17,19} In some individuals, the reactions develop earlier, progress at an accelerated pace and are more severe than after comparable doses of roentgen rays alone (Fig. 1). Actinomycin D can also reactivate "latent" radiation effects in tissues which have been previously irradiated but which have

returned to a normal appearance in the interval (Fig. 2).³

This combination of treatment modalities has been used as a part of extensive investigations of carcinolytic substances under the direction of Sidney Farber.⁸ One of the largest groups of patients so treated is composed of children with Wilms' tumor. Many have widespread metastases, that is, with deposits in at least two lobes of the lungs or in two or more organ systems, and it is to this group that further discussion will be limited.

TECHNIQUE

The details regarding chemotherapeutic management have already been reported.^{9,10}

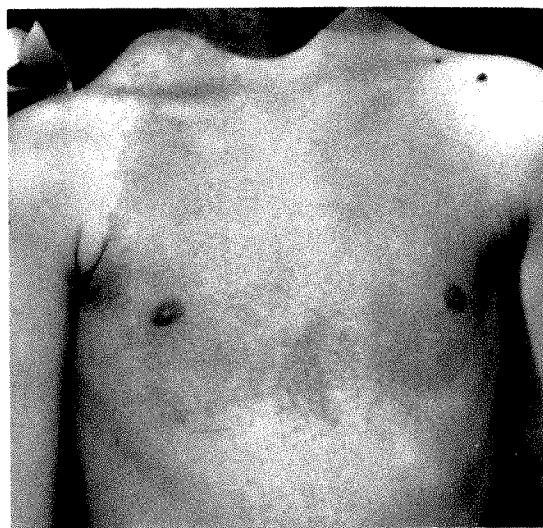


FIG. 1. A six year old girl in whom the cutaneous roentgen-ray reaction was enhanced by the intravenous administration of actinomycin D. The first blush appeared after a skin dose of 520 r. At the time this photograph was taken, the estimated skin dose was 780 r.

* From the Department of Radiology and the Children's Cancer Research Foundation, the Children's Medical Center, and the Department of Radiology, Harvard Medical School, Boston, Massachusetts. This investigation was supported in part by a grant from the National Institutes of Health, USPHS #CY3335.

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The roentgen-ray treatment portals are designed to ensure coverage of all disease-bearing tissue without, at the same time, unnecessarily irradiating any adjoining normal developing structures. The technical factors used are: 250 kv. (constant potential), 0.4 mm. Sn, 0.25 mm. Cu, 1 mm. Al added filtration (half value layer of 2.7 mm. Cu), 15 ma., 50 cm. target-skin distance. When widespread lung metastases are present, opposing anterior and posterior chest portals are employed.

The first day, a tumor dose of 75 r is delivered (as calculated at the midplane of the thorax). If well tolerated, this amount is increased to 150 r, which is then delivered daily to alternating fields until a total depth dose of 1,200 r is attained. The treatment portals are not restricted to those areas of involvement demonstrable on roentgenographic examination. Metastases in peripheral subpleural locations occur frequently and, when there are multiple lung deposits, are presumed to be present whether visible roentgenographically or not. All the lung parenchyma from the extreme apex to the most inferior recess of the thoracic cavity is included. It is our belief that the results are better when all potentially involved sites within the lungs are treated in the initial course of combined therapy.

The shape of the portals is adjusted wherever possible to exclude normal structures from unnecessary irradiation, a point of particular importance in children. The proximal humerus and glenoid fossa of each shoulder is shielded with 2 mm. of lead. The spinal cord and the skin at the midline of the back also are protected. A strip of lead 2 mm. thick and 1 cm. wide is employed for the average patient. The lead usually is placed directly on the skin and held in position with pieces of cellophane tape. The shoulder blocks are used for both the anterior and posterior fields, but the spinal cord shield is applied only when the posterior field is being treated. Adequacy of protection and of coverage is checked by roentgenograms

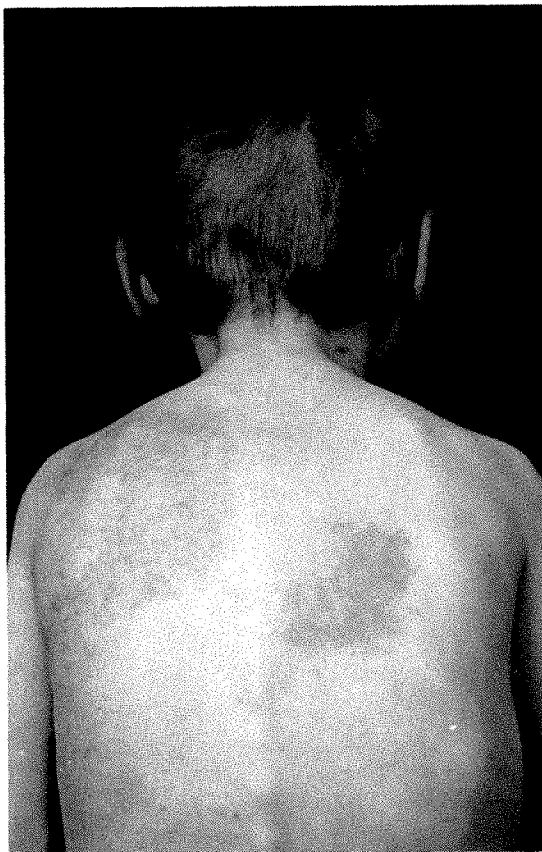


FIG. 2. A four year old boy in whom there was reactivation of latent radiation effects in the skin. This child received combined roentgen-ray and actinomycin D therapy for left midlung and right paracardiac metastases. The skin reddened but soon returned to normal. Hepatic metastases became evident three months later, and roentgen-ray treatment of the liver combined with chemotherapy was started. Simultaneously with the administration of actinomycin D, reactions reappeared that coincided in size and distribution with the earlier treatment portals.

(Fig. 3) obtained for each portal employed. They are taken with the child in the treatment position and on the therapy table. The exposures are made using the therapy tube but with the factors reduced appropriately for a diagnostic technique. These films provide a permanent record of the areas treated.

Roentgen therapy of the thorax and of the entire abdomen becomes necessary at times as, for example, in a patient with bilateral pulmonary metastases in whom

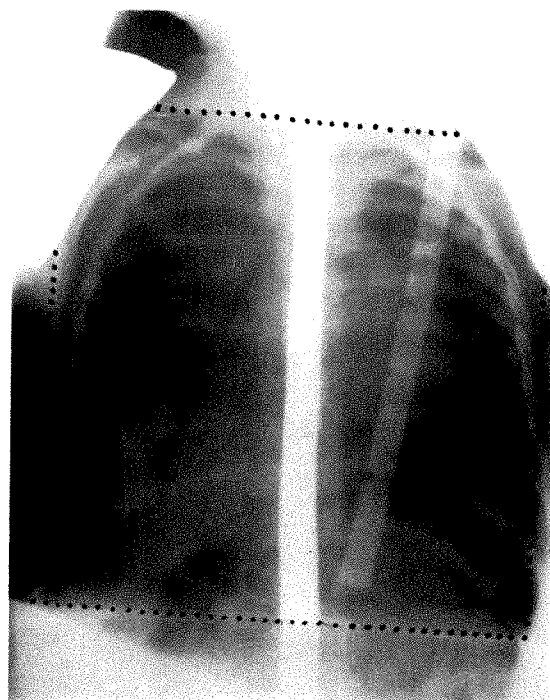


FIG. 3. Posterior treatment portal employed for Wilms' tumor metastases in the lungs. Lead shields protect the shoulders, midline of the back and spinal cord. A double exposure technique is used in taking the roentgenogram. The smaller, darker image (dotted lines) is that of the treated area. The larger, lighter exposure includes more anatomic landmarks to assist in orientation. A lead ruler notched at 1 cm. intervals is placed on the entry skin surface. It provides an easy means of correction for magnification when changes in size or alignment of the field are to be made, as in this case where minor changes were necessary in the positioning of the shoulder protectors and in the width of the field to the left.

the primary tumor ruptured during surgical removal. It usually has been possible to proceed with chemo- and roentgen therapy (at the rate of 150 r tumor dose per day to each area) without precipitating excessive or irreversible leukopenia or thrombocytopenia. The peripheral white blood cell count of an occasional patient falls below 2,000 per cubic mm. or the platelets below 150,000 per cubic mm. Combined treatment is then interrupted for a brief period to allow the patient to recover. Therapy has been resumed and completed in virtually every case.

Wilms' tumor metastases to organs other than the lungs occur infrequently and then almost always after pulmonary lesions have first become evident. The liver, skeletal system, lymph nodes, brain, and spinal cord figure prominently as sites of possible involvement. Combined treatment with roentgen-ray doses of up to 3,000 r has been used for liver and central nervous system involvement, but only temporary control has resulted. Recurrence within four to twelve weeks has been the rule. More encouraging responses have been obtained in the few patients with metastases to lymph node or bone in addition to the pulmonary lesions. Continuing survival without recurrent disease for long periods—twenty months or more—has been obtained in isolated instances. Roentgen-ray doses of 1,200–1,500 r at depth are used. The treatment portal again is designed to cover all tissues known to be involved together with an adequate margin, but all normal structures which can be avoided are scrupulously excluded from the field.

Some patients require re-treatment of the thorax because of recurrent pulmonary metastases. An additional course of roentgen therapy and actinomycin D is then given. The roentgen-ray dose is the same as before if three months or more have elapsed. When the interval is shorter, a depth dose of 800 r is given, since the addition of another 1,200 r can lead to radiation pneumonitis. Some children respond favorably to a second course of therapy with disappearance of metastases and prolonged survival without recurrence. Occasionally, the majority of lesions disappears but one or two foci prove refractory to treatment. Surgical removal may then become advisable. The prior roentgen-ray therapy does not preclude surgical intervention, which is sustained well by these children. Segmental resections have at times been successful in the eradication of the remaining disease.

RESULTS

Farber and co-workers¹⁰ have reported

the therapeutic results obtained in 13 children with widespread metastases who received combined treatment. Five (38 per cent) remained free of disease for periods of two years or more after treatment. These patients, all of whom had roentgen irradiation of the chest, appeared clinically well, without growth disturbance of the bony thorax and without overt impairment of pulmonary function.

SUMMARY

Roentgen-ray effects in normal and neoplastic tissues of mice are enhanced by actinomycin D. In humans, skin and mucous membranes sometimes react earlier and more strongly to combined treatment than to comparable doses of roentgen rays alone. Actinomycin D alone may reactivate latent radiation effects in skin which has been previously irradiated but which has returned to a normal appearance. Encouraging results using combination therapy have been obtained in children with widespread metastases from Wilms' tumor. The roentgen therapeutic aspects of their management are discussed.

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PRIMARY CARCINOMA OF THE PITUITARY*

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BENIGN pituitary adenomas represent approximately 15 per cent of all intracranial tumors, with massive extension out of the sella turcica occurring in about 10 per cent of these patients. Primary carcinoma of the pituitary, however, is a rare occurrence.^{1,2,10,12} Such rarity of true malignant pituitary adenomas is surprising when one considers the frequency of carcinomas of other endocrine organs, and the relatively common occurrence of carcinomas of the oral cavity from which the anterior pituitary is derived.

A review of the records of the University of California Hospital, San Francisco, shows that in the ten year period from 1950 through 1959, 93 patients with pituitary adenomas were seen. Of these, 47 were considered benign chromophobe adenomas of which 20 were explored and proved histologically. There were 33 eosinophilic adenomas with acromegaly and 5 were thought to be basophilic adenomas. Eight patients were initially diagnosed as having pituitary carcinomas. Of this group, however, only 4 patients were accepted by us as representing true pituitary carcinomas since definite evidence of invasion of adjacent nervous structures or bone, or cellular anaplasia with frequent mitoses could not be demonstrated in the others.

REPORT OF CASES

CASE 1. This thirty-nine year old white woman with combined fibrosarcoma and adenocarcinoma of the pituitary had an eleven year history of acromegaly. She had had two courses of roentgen therapy ten years before the diagnosis of malignancy.

The patient was first seen at the University of California Hospital in November, 1946 at the age of twenty-eight years, complaining of progressive fatigue, episodes of blurred vision, amenorrhea of five months' duration, and an

increase in the size of her feet since pregnancy four years previously.

Physical examination revealed typical acromegalic, coarse facial features with prominent supraorbital ridges, and unusually large hands and feet. All other findings of the general and neurologic examinations, as well as visual field studies, were normal.

Roentgenograms of the skull showed a depressed floor of the sella turcica with slightly thinned and straightened posterior clinoids (Fig. 1 A).

The results of routine laboratory studies were normal except for slight elevation of the serum phosphorus level.

A prolonged course of estrogen therapy was instituted and she was followed in the clinic until May, 1947. At that time a first course of roentgen therapy was given with a total estimated tumor dose of 2,570 r being delivered in thirty-two days through two lateral 6×6 cm. portals, using both 1,000 kv. and 200 kv. with half value layers of 9 mm. Cu and 1.32 mm. Cu, respectively.

Following irradiation she continued to have headaches and slight elevation of the serum phosphorus level. A second course of radiation therapy was therefore given in November, 1947 with a tumor dose of 1,340 r in sixteen days through two lateral 6 by 6 cm. fields, using 200 kv., 1.32 mm. Cu half value layer.

The patient's condition was then satisfactory for ten years. In April, 1957 she was readmitted to the hospital because of headache, lethargy, and visual changes of a month's duration. The only abnormalities found on physical examination were the acromegalic features and bitemporal field defects, most marked in the superior quadrants. The rest of the neurologic examination and appearance of the optic disks were normal. Routine laboratory studies including cerebrospinal fluid proteins were normal.

Skull roentgenograms in March, 1957, a month before re-admission to the hospital (Fig. 1 B) had shown the enlarged sella turcica unchanged from that observed during the exami-

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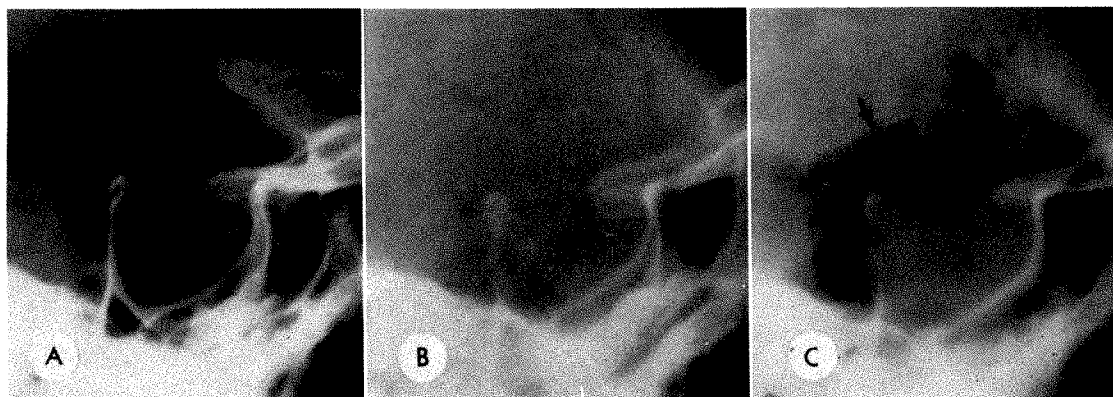


FIG. 1. Case I. (A) November, 1946: Enlarged sella turcica with depression of floor and thinning of dorsum sellae. (B) March, 1957: Slight increase of erosion of base of dorsum sellae. (C) April, 1957: Further erosion with apparent discontinuity of the dorsum sellae. Note small suprasellar extension and retention of relatively sharp cortical margins of floor.

nation done ten and one-half years previously, with, however, a slight increase in thinning of the base of the dorsum sellae. Skull roentgenograms repeated at the time of admission showed further bone erosion of the dorsum sellae at its base. A pneumoencephalogram showed slight suprasellar extension of the tumor (Fig. 1 C).

On April 26, 1957, a right frontal craniotomy revealed a fleshy tumor projecting out of the sella turcica, displacing both optic nerves and internal carotid arteries laterally. A portion of the tumor lying lateral to the optic nerves could not be removed.

The tumor was composed of a stroma of small spindle cells with hyperchromatic, pleomorphic nuclei showing occasional mitotic figures. Scattered throughout this stroma were numerous nests and cords of larger cells with granular eosinophilic cytoplasm. The nuclei were hyperchromatic and pleomorphic and showed prominent mitotic activity. The lesion was considered to be a combined fibrosarcoma and eosinophilic adenocarcinoma of the pituitary (Fig. 2).

Following surgery, the visual fields showed an initial improvement, but one month later the vision suddenly deteriorated. The patient, therefore, received a third course of roentgen therapy with a total tumor dose of 4,900 r delivered in fifty-eight days through two lateral and one anterior 5 by 5 cm. port, using 1,000 kv. with 2.4 Pb half value layer. During this treatment the visual fields progressively improved. There was slight residual flattening of both upper temporal quadrants.

She was then without symptoms until November, 1957 when continuous severe headaches, nausea, and vomiting began. She became increasingly lethargic and died two weeks later. A postmortem examination was not performed.

CASE II. This fifty-six year old white man with chromophobe adenocarcinoma breaking through its capsule had a rapid return of symptoms following surgery and radiation therapy. Death occurred six weeks after a second exploration.

The patient was first admitted to the University of California Hospital in September, 1956 complaining of decreased vision in the left eye of two months' duration and slight frontal headaches. The only abnormal physical finding was a left temporal hemianopsia. No clinical or laboratory evidence of pituitary hypofunction was found.

Roentgenograms of the skull showed the sella turcica to be slightly enlarged with demineralization of the floor and posterior clinoids (Fig. 3). Bilateral carotid arteriograms showed no definite abnormality. Routine laboratory studies were normal. The cerebrospinal fluid protein was 93 mg. per cent.

A left frontotemporal craniotomy in September, 1956 revealed a friable red neoplasm projecting out of the sella turcica medial and anterior to the left anterior clinoid, displacing the left optic nerve superiorly. A subtotal removal of the tumor was accomplished, and the left optic nerve was decompressed. Microscopically, the tumor cells contained small

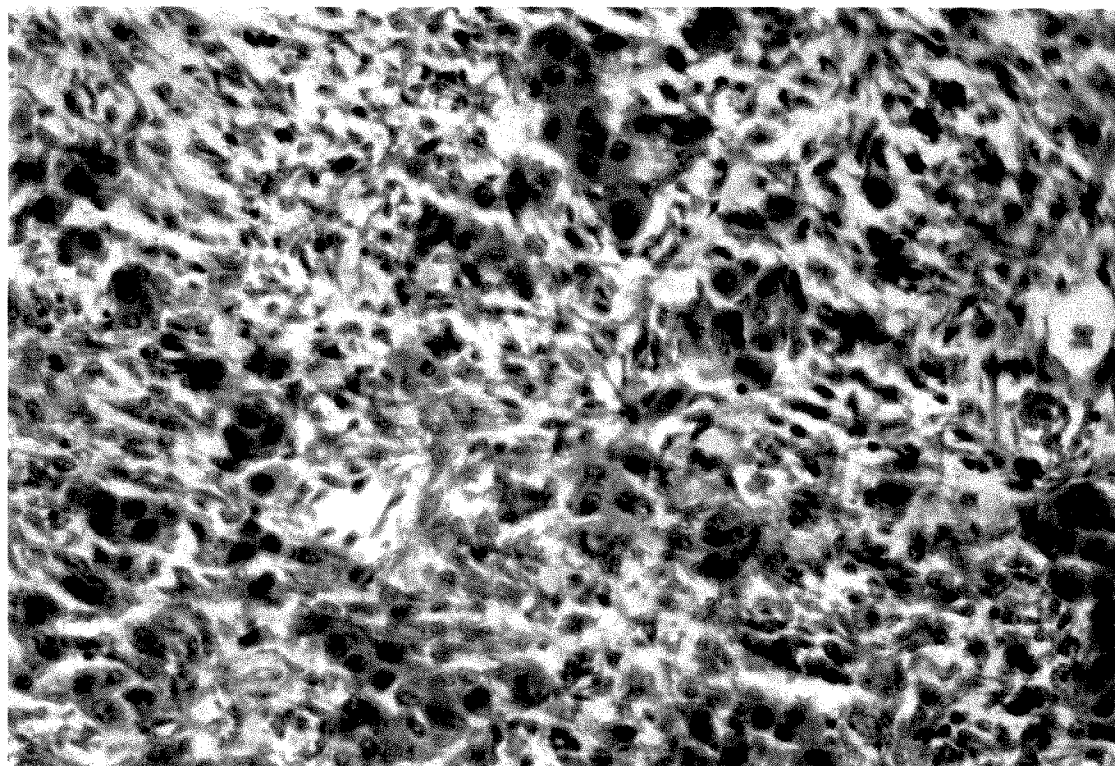


FIG. 2. Case I. Combined fibrosarcoma and eosinophilic adenocarcinoma of the pituitary.

amounts of cytoplasm with pleomorphic nuclei showing frequent mitotic figures (Fig. 4). The cells lay in small nests surrounded by a stroma of branching strands of connective tissue. A diagnosis of anaplastic malignant chromophobe carcinoma of the pituitary was made.



FIG. 3. Case II. Slight increase in sellar size with demineralization of floor and base of dorsum sellae.

The patient received postoperative roentgen therapy with an estimated total tumor dose of 5,000 r delivered in forty-seven days through two lateral and one frontal 5 by 6 cm. portal, using 1,000 kv., 3.2 mm. Pb half value layer. The vision improved considerably with a small, left upper temporal field defect remaining.

In May, 1957 the patient again noted gradual diminution of vision in his left eye. The left pupil was dilated and fixed, and a complete left temporal hemianopsia was present. Vision in the left nasal field was markedly impaired and limited to light perception and recognition of large objects. Slight atrophy of the left optic nerve was noted. The remainder of the findings on neurologic examination was negative.

At re-exploration, a fleshy, vascular, friable tumor which had broken through its capsule was found. It elevated and displaced the chiasm posteriorly and flattened the left optic nerve. The tumor extended approximately 2 cm. anterior to the chiasm. Subtotal removal with decompression of the left optic nerve was carried out. Microscopic examination showed sheets of cells with hyperchromatic, pleomorphic nuclei with frequent mitoses. These cells tended

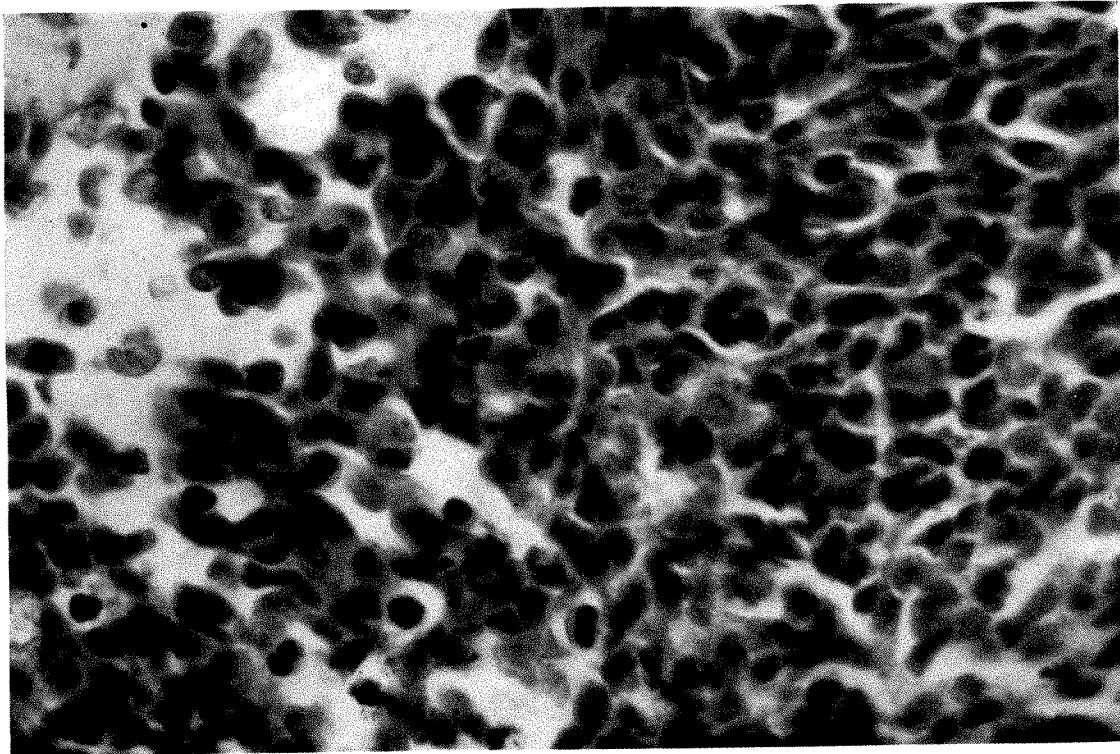


FIG. 4. Case II. Marked pleomorphism of nuclei with prominent mitotic activity.

to be arranged around small blood vessels. The tumor was again diagnosed as a pituitary chromophobe carcinoma.

Following this second operation, no change in the visual fields occurred. Two weeks later, apathy, incontinence, left hemiparesis, and disorientation began to develop. He died six weeks after the second operation. A postmortem examination was not performed.

CASE III. This fifteen year old white boy presented a three year history of headache and visual complaints. A chromophobe adenocarcinoma invading midbrain, pons, and right cavernous sinus was found. Malignancy was established only at a third craniotomy following two subtotal resections of benign adenomas and one course of roentgen therapy. A rapid increase in the size of the sella turcica occurred immediately preceding the diagnosis of carcinoma.

The patient, born in November, 1944, was well until the spring of 1956 when he complained of left-sided frontal headache and retro-orbital pain. Examination at another hospital revealed a left centrocecal scotoma and

suggestive hypopituitarism. Skull roentgenograms showed slight enlargement of the sella turcica with bony erosion at the base of the dorsum sellae and posterior displacement of the posterior clinoids. A pneumoencephalogram disclosed a suprasellar mass displacing the anterior portion of the third ventricle (Fig. 5 *A*). A right frontal craniotomy performed in June, 1956 revealed a histologically benign chromophobe adenoma. The visual field defect cleared following a course of roentgen therapy with an estimated tumor dose of 3,000 r delivered in thirty days, using 200 kv. with a half value layer of 2.07 mm. Cu.

The boy was then well until March, 1958, at which time he developed a right oculomotor palsy with dilated pupil, ptosis, and diplopia. Roentgenograms of the skull (Fig. 5 *B*) again showed enlargement of the sella turcica with slight depression of the floor and posterior displacement of the posterior clinoids. No significant change was noted from the examination made two years previously. Re-exploration in April, 1958 disclosed a granular, reddish tumor protruding out of the pituitary fossa and growing up beneath and between the optic nerves.

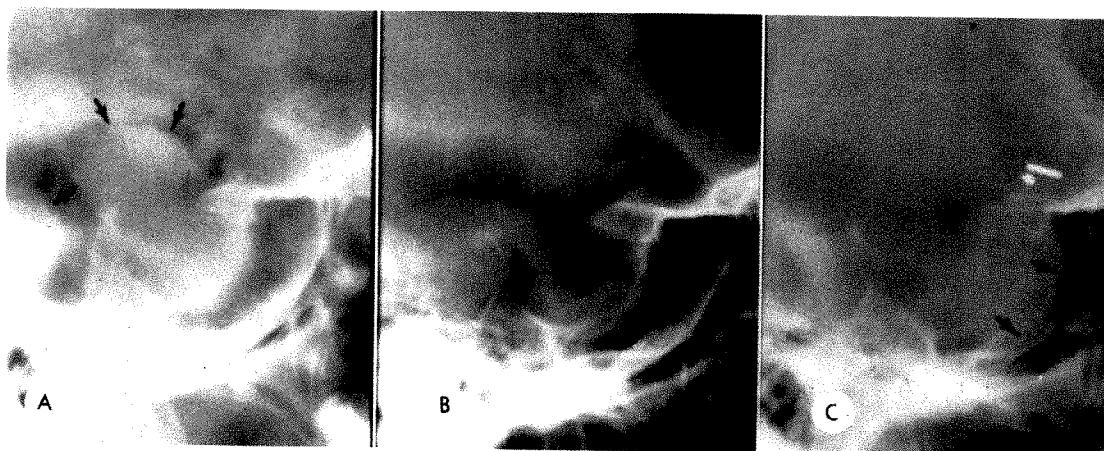


FIG. 5. Case III. (A) June, 1956: Suprasellar extension is observed on a pneumoencephalogram. Slight depression of the floor of the sella turcica and backward tipping of posterior clinoids are also noted. (B) April, 1958: Appearance of the sella turcica essentially unchanged from previous examination. (C) July, 1958: Marked depression of the floor of the sella turcica with encroachment of sphenoid sinus and further decalcification of dorsum sellae is seen.

Total excision was not attempted. The histologic examination again showed a benign chromophobe adenoma with occasional mitoses. The entrance of the third nerve into the cavernous sinus could not be demonstrated and the cause for the ophthalmoplegia was not discovered.

Because of lack of improvement following the second operation, the patient was referred to the University of California Hospital. Physical examination revealed an uncooperative, apprehensive boy with a slurred speech. Almost total right ophthalmoplegia with ptosis and a dilated pupil was found. The corneal reflex was absent on the right. Altered light-touch sensitivity over the right face was disclosed and a central facial weakness was present on the left. The right optic disk appeared normal, whereas the left was definitely atrophic. A bitemporal visual field defect was noted, most dense in the lower quadrants. The patient had a swaying, unsteady, broad-based gait.

Roentgenographic examination of the skull (Fig. 5 C) now showed a definite change in the sella turcica as compared to the previous examination done three months earlier. There was marked increase in the depression of the floor of the sella turcica with consequent decrease in depth of the sphenoid sinus. Laboratory studies, including cerebrospinal fluid proteins, were normal.

On August 6, 1958 a right frontoparietal craniotomy was performed with subtotal removal of a reddish, lobulated invasive tumor

about the right internal carotid artery, both optic nerves, the optic chiasm, and the right optic tract. Posteriorly, the tumor extended beneath the hypothalamus and third ventricle. The tissue consisted of a collagenous stroma with nests of cells varying in size and shape. Nuclei showed pleomorphism and prominent mitotic activity. These findings were interpreted as representing a malignant chromophobe adenoma.

Following this third operation, the patient received a second course of irradiation with an estimated tumor dose of 5,300 rads delivered in thirty-nine days through two lateral 6.25 by 6.25 cm. portals, using the 70 mev. synchrotron. The radiation therapy was interrupted because of increased intracranial pressure from aqueduct obstruction by the pituitary tumor. This pressure was relieved by a ventriculo-auricular shunt operation. The patient's condition slowly declined, however, and he died in another hospital in April, 1959.

The postmortem findings showed a moderately firm yellow-brown tumor occupying the sella turcica and extending intradurally to invade the right side of the midbrain and pons (Fig. 6). The tumor extended laterally into the right cavernous sinus. The inferior surface of the right cerebellar hemisphere was infarcted, apparently from tumor obstructing the right anterior inferior cerebellar artery. Microscopic examination showed that the tumor had invaded and partly replaced the pons. Tumor cells were found in the fourth ventricle (Fig. 7).

The cerebellum, cranial nerves, leptomeninges, and dura were also involved.

CASE IV. This twenty-seven year old white woman with acromegaly died following exploration. A large malignant adenoma invading the fifth nerve ganglion with a metastatic nodule in the hippocampal gyrus was found.

This patient was admitted to the University of California Hospital in September, 1959 complaining of pain over the left eye and of failing vision.

Except for amenorrhea following the birth of a child in 1957, she was in good health until June, 1959. At that time she began to have intermittent, throbbing headaches over the left eye. She also noted enlargement of the hands and feet, and fullness of the face.

The physical examination showed a slightly obese, confused Mexican woman with typical acromegalic features, breast enlargement with galactorrhea, and equivocal evidence of hypothyroidism. The neurologic examination revealed marked bitemporal field defects, although accurate mapping of these defects was difficult because of the patient's confusion and inattention. The disk margins were slightly blurred and the left disk was pale. The cranial nerves were otherwise normal. Deep tendon reflexes were hypoactive but equal. The rest of the neurologic examination was normal.

Roentgenograms of the skull showed the scalp and calvarium to be thicker than normal. Marked ballooning of the sella turcica with deepening of the floor and posterior displacement and thinning of the dorsum sellae and the posterior clinoids were noted (Fig. 8). The basal view suggested erosion of the greater wing of the sphenoid on the right.

A left frontotemporal craniotomy revealed a purplish, vascular suprasellar mass. The tumor was noted to extend laterally into the middle fossa and was deemed inoperable.

Postoperatively the patient responded poorly. The next day her temperature rose to 40° C. and she died that evening.

Postmortem examination of the brain showed a large lobular, grayish, partly necrotic tumor arising from the sella turcica. The tumor, measuring 6 by 3 cm., indented and compressed the base of the frontal lobes, occluding the major part of the right anterior horn and foramen of Monro. The optic nerves and chiasm were greatly compressed. A separate smaller tumor nodule was attached to the meninges near the right hippocampal gyrus, compressing the



FIG. 6. Case III. Specimen of the massive tumor which invaded the right side of the pons and mid-brain.

hippocampus (Fig. 9). The left ventricle and midline structures were displaced to the left. The area of the right middle cerebral artery showed evidence of acute infarction (Fig. 10). Microscopically, the tumor revealed patternless sheets of small polygonal cells with spherical nuclei varying in size and chromatin content and showing scattered mitotic figures. Many cells showed vacuolation of the cytoplasm resulting in large foam cells. No definite chromophil granules were noted in the tumor cells. Where it adjoined the cavernous sinus, the tumor had penetrated its capsule to invade the roots of the trigeminal nerve (Fig. 11). It did not, however, invade the brain tissue, causing only displacement and pressure changes in the caudate nucleus and basal cortex of the frontal lobes.

DISCUSSION

PATHOLOGY

There still is no definite agreement as to what constitutes a malignant pituitary adenoma, despite the work done by many investigators.⁷ In our studies we have used

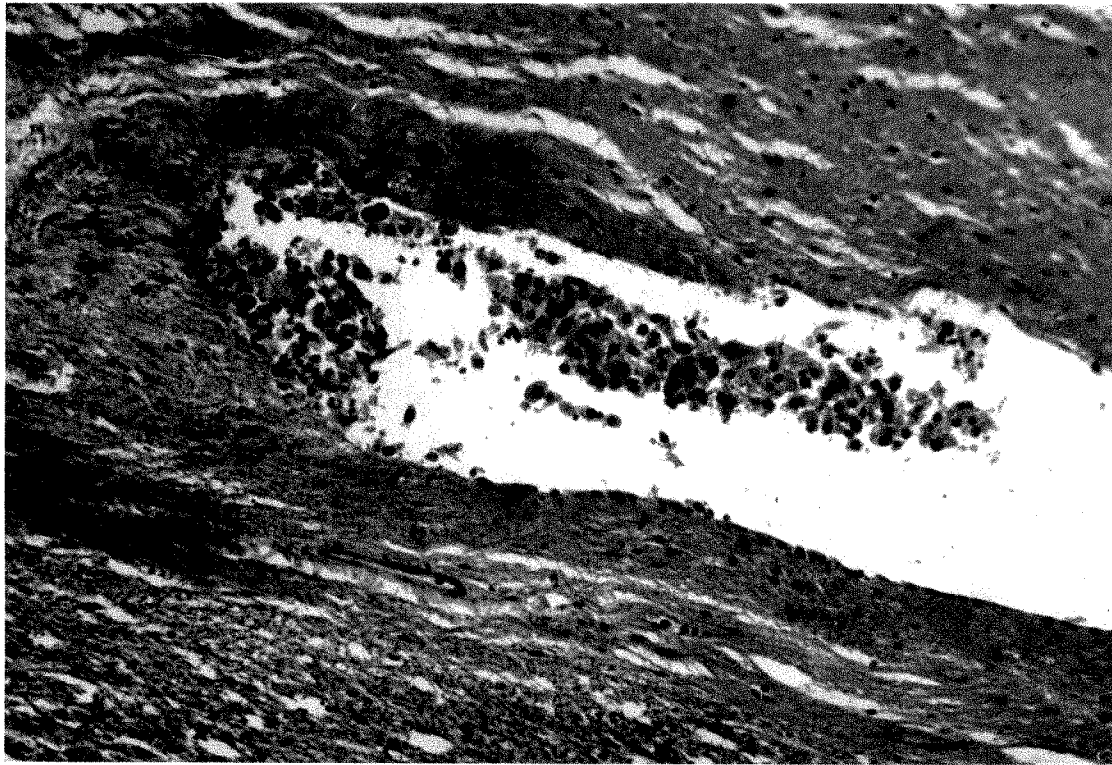


FIG. 7. Case III. Pleomorphic tumor cells which invaded the fourth ventricle.



FIG. 8. Case IV. Enlarged sella turcica with downward displacement of floor and thinning of dorsum sellae.

the criteria outlined by King,⁸ Jefferson,^{5,6} and Kraus.⁹ We agree with these authors that a pituitary adenoma is malignant if it bursts its capsule to invade adjacent nervous structure or bone, or if it shows histologic evidence of malignancy, *i.e.*, loss of alveolar arrangements and anaplasia with hyperchromatic pleomorphic cells showing frequent mitoses. Specific cell granules are often not present in pituitary carcinoma. The differentiation of massive benign adenomas from infiltrating malignant adenomas may be difficult on gross examination. Benign tumors may attain massive size and may be solid or cystic. Unlike pituitary carcinomas, large benign adenomas usually take the path of least resistance and expand superiorly into the middle or anterior fossa to displace the hypothalamus, third ventricle, frontal, or temporal lobes. Occasionally, by slow, progressive growth, a benign adenoma still within its capsule may expand downward into the nasopharynx, anteriorly into the paranasal sinuses, or laterally, compressing the cavernous sinus



FIG. 9. Case IV. Massive subfrontal tumor mass. Note separate tumor nodule on right hippocampal gyrus.

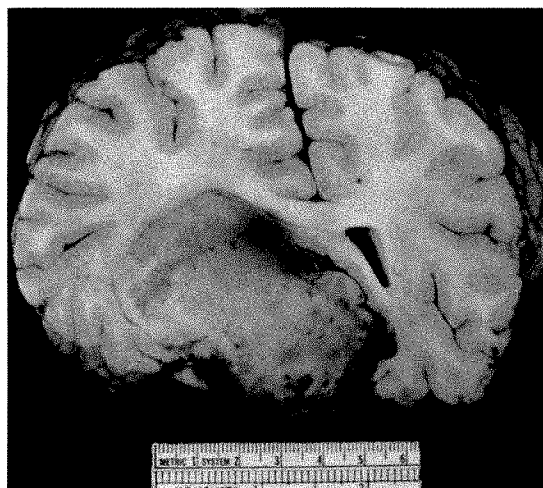


FIG. 10. Case IV. Specimen showing the subfrontal extension of the large tumor mass which displaced the ventricular system to the left.

structures. Invasive pituitary carcinomas, on the other hand, readily destroy adjacent structures and may often spread laterally to invade the cavernous sinuses. The presence of mitoses, although indicating active growth, is in itself not diagnostic of malignancy since occasional mitoses may be seen in benign adenomas. Metastases by implantation on the meninges via the cerebro-

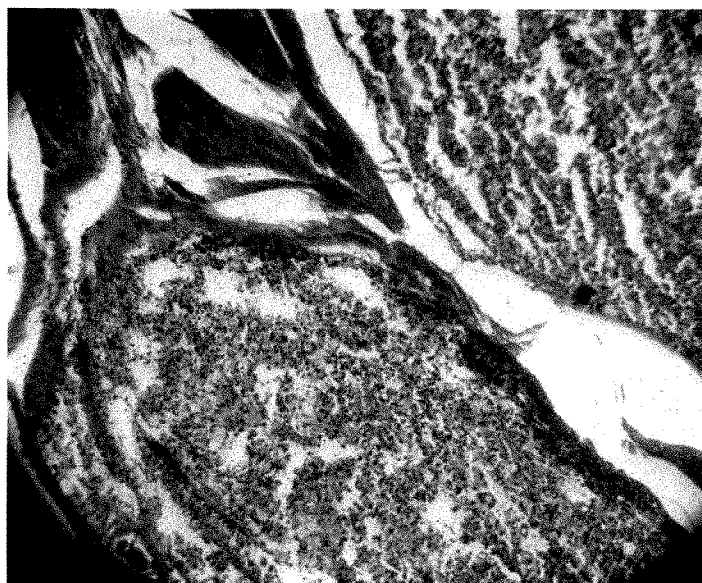


FIG. 11. Case IV. Roots of trigeminal nerve invaded by pleomorphic tumor cells.

spinal fluid, as in Case IV, have rarely been reported.^{3,4} The extreme rarity of dissemination outside the cerebrospinal axis probably relates to the lack of anatomic proximity to lymphatics and does not exclude the malignant nature of the tumor.⁶ The diagnosis of malignancy is, therefore, based on (a) the usual histologic criteria of malignancy; *i.e.*, loss of normal cellular pattern, presence of pleomorphism, anaplasia usually with absence of specific cell granules and mitoses, and (b) evidence of invasion.

CLINICAL ASPECTS

The clinical aspects of malignant pituitary tumors have been well described by Jefferson⁶ and King.⁸ They stress the frequency of invasion of the cavernous sinus by pituitary carcinomas causing trigeminal symptoms often associated with involvement of the third, fourth, or sixth cranial nerves. In our series, however, only one patient (Case III) showed clinical evidence of cavernous sinus involvement with ophthalmoplegia and partial involvement of the fifth and seventh cranial nerves. Visual field defects, noted in all of our patients, are not a helpful differential point since they are common in both benign and malignant adenomas. Similarly, the presence of optic atrophy and pituitary dysfunction is common in both types. Jefferson⁶ stated that the incidence of malignant change in eosinophilic adenomas may be higher than in the chromophobe group and, curiously, all of his malignant eosinophilic adenomas were in females. It is, therefore, of interest that in our small series, 2 of the patients were acromegalic, and both were women. In Jefferson's series of 14 patients, the largest single series of reported cases, the length of time between the onset of symptoms and the patient's death varied from three months to seventeen years. One may postulate that the long survival in some patients may be due to late malignant change in an initially benign adenoma. Thus, the tumor in Case I may have been a benign eosinophilic adenoma for ten years with malignant change occurring just before the recur-

rence of clinical symptoms, approximately six months prior to death. The course in our other patients varied from twelve to thirty-six months and is thus much shorter than that of benign adenomas. The lack of sustained improvement following radiation therapy (Cases II and III) might suggest the presence of a malignant pituitary adenoma.

The relationship between roentgen therapy to the pituitary and malignant degeneration remains doubtful. The rarity of reported malignant adenomas when compared with the large number of patients who have received pituitary irradiation suggests the absence of a causal relationship. In Case I, however, the association of fibrosarcoma and eosinophilic adenocarcinoma of the pituitary occurring ten years after two courses of roentgen therapy may implicate the radiation therapy as a causal factor of the sarcoma. This case appears to have been unique and resembled the 3 cases of combined fibrosarcoma and chromophobe adenoma reported by Terry *et al.*¹³ Their 3 patients all received repeated courses of irradiation with total tumor doses of about 6,500 to 7,500 r. The time interval between the initial roentgen therapy and the diagnosis of fibrosarcoma varied from two to twelve years. Therefore, although most uncommon, the possibility of radiation-induced pituitary malignant tumors cannot be excluded.

ROENTGEN ASPECTS

The sellar changes associated with intrasellar tumors have been well described by Mahmoud.¹¹ The roentgenologic differentiation of malignant from benign pituitary adenomas, however, remains uncertain. In 2 of our patients (Cases I and III) the change in the appearance of the sella turcica immediately prior to the diagnosis of pituitary malignancy suggested rapid growth of the tumor. This may suggest the malignant nature of an adenoma¹¹ but it is not diagnostic since benign tumors may also expand rapidly, causing similar changes. Moreover, large benign adenomas not only

cause enlargement of the sella turcica but may also cause pressure erosion of adjacent bony structures, such as widening of the superior orbital fissure or eccentric erosion of the optic foramen. Occasionally, benign adenomas may cause pressure erosion of the sphenoid sinus and project into the nasopharynx. Bone eroded by such pressure has a sharp cortical margin, while bone destroyed by tumor invasion generally has an irregular mottled appearance. In our series of patients, however, no definite irregular bone erosion was noted; this roentgenologic finding, therefore, could not be used as an aid in the differentiation of malignant from benign pituitary tumor.

Although malignant adenomas tend to attain large dimensions, size alone is not conclusive of malignancy. Histologically proved benign adenomas, often cystic and without invasion, have been seen to attain huge size. It is important to know the preoperative extent of the tumor since this relates directly to operative mortality. The massive size of the tumor may not be suspected on clinical examination (Case IV). For this reason, pneumoencephalography with the fractional technique should precede any therapeutic approach. Carotid angiography is not as useful a procedure in determining the extent of the tumor but is employed to exclude vascular abnormalities such as aneurysm. Carotid arteriography was performed in 3 of the patients in this series (Cases I, II and III). In none of these was a tumor blush recognized nor was any appreciable lateral displacement of the internal carotid arteries in the cavernous sinus demonstrated. In this group, arteriography was therefore not helpful in the differentiation of benign from malignant tumors.

It is of interest that in a review of patients with proved metastatic carcinoma to the pituitary from various primary sites no changes in the sella turcica were noted. This correlates with the histologic findings of small, often microscopic, secondary deposits in the pituitary which fail to attain large size.

SUMMARY

Reports of 4 patients with malignant adenomas of the pituitary (2 chromophobe and 2 eosinophil) are presented. The diagnosis of pituitary carcinoma depends on the demonstration of invasion of adjacent nervous structures or on the presence of marked cellular anaplasia and mitotic activity. The clinical diagnosis may be suspected when there is evidence of rapid growth of the tumor, particularly when associated with cavernous sinus syndrome. Unlike previous reports which stressed the frequency of cavernous sinus syndrome, only 2 of our patients showed such a finding. One acromegalic patient who had had two courses of roentgen therapy ten years previously showed a combined fibrosarcoma and eosinophilic adenocarcinoma, suggesting a possible complication of radiation therapy.

The roentgenologic features which may suggest a diagnosis of pituitary carcinoma are discussed.

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We wish to thank Dr. Nathan Malamud of the Department of Pathology, Langley Porter Neuropsychiatric Institute, for his help in reviewing the pathologic material in this study.

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RETICULUM CELL SARCOMA OF BONE*

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IT IS usual to make a distinction between reticulum cell sarcoma originating in soft tissue and that occurring primarily in bone.

Craver and Copeland,³ in reviewing 164 cases of lymphosarcoma, reported 17 cases in which bone involvement occurred. Only one of these appeared to be primary in bone (scapula), and this patient died from generalized disease within a year. All of the cases with bone involvement were classified as reticulum cell sarcoma. The authors commented on the greater incidence in patients over forty years of age, the predominance of males in a ratio of 1.6:1, the inevitable progression of the disease with metastases to structures such as spleen, liver, and lymph nodes, and the probability of death within three years of the onset of the disease. Five years later, however, Parker and Jackson⁹ presented a series of cases having lesions of bone histologically identical with reticulum cell sarcoma of the soft tissues, but following an entirely different clinical course. These occurred generally in patients less than forty years of age and tended to involve initially but one bone, usually of the long tubular variety. Characteristically, these were associated with a long clinical course during which the patient's general condition remained good. Since that time several articles have appeared reporting small numbers of cases^{10,11} as well as a few larger series.^{4,6} A discussion of these cases as part of the larger problem of lymphosarcoma in children has also appeared.¹²

On reviewing the reports of localized reticulum cell sarcoma of soft tissue and of bone which have appeared in the literature and the 8 cases forming the basis of the present report, the question arises whether such a clear distinction is justifiable.

The following 8 cases are from the files of three hospitals with which the author has been associated. All have been carried on the pathologic and clinical records as primary reticulum cell sarcoma of bone.

REPORT OF CASES

CASE I. Male, aged fifty-five years. This patient was initially seen with a pathologic fracture of the humerus. There was a history of approximately three months' duration of increasing pain and limitation of movement in the region of the right shoulder. Roentgenograms demonstrated a 4 cm. osteolytic lesion involving the proximal humeral shaft (Fig. 1). No

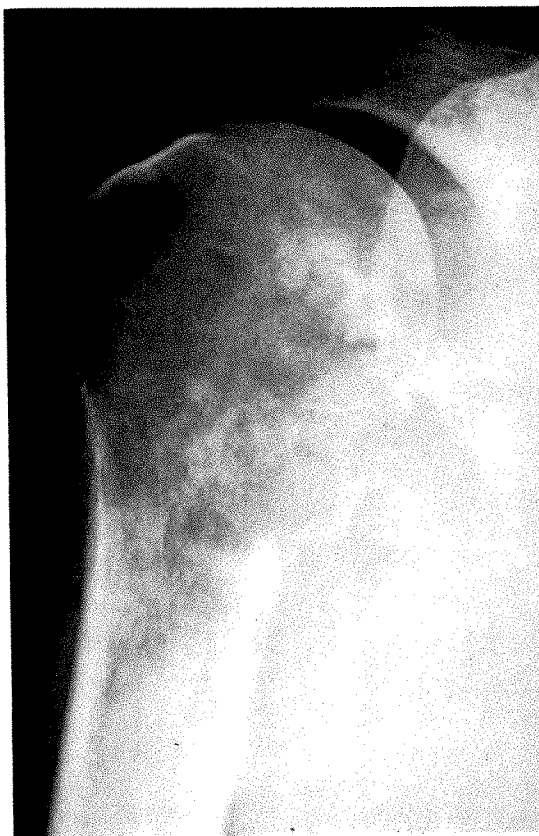


FIG. 1. Case I. Poorly circumscribed osteolytic lesion with cortical destruction and fracture.

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lymphadenopathy was present; the patient's general health was good. Open biopsy was performed. The diagnosis was reticulum cell sarcoma in bone. Roentgen therapy resulted in marked regression of the lesion and healing of the fracture. Two months after completion of treatment, the lesion showed progression. The patient remained in good general health and a second course of radiation was given without demonstrable roentgen change. Bone survey revealed no further lesions. This status was maintained for two months. However, during the next three months the patient's condition deteriorated very rapidly and he died. Permission for autopsy could not be obtained.

CASE II. Female, aged sixty-four years. This patient had no complaints until she injured her left humerus in a fall. Roentgenograms revealed a pathologic fracture through a localized osteolytic lesion in the mid-shaft (Fig. 2). Open biopsy of the lesion was interpreted as reticulum cell sarcoma. There were no other complaints

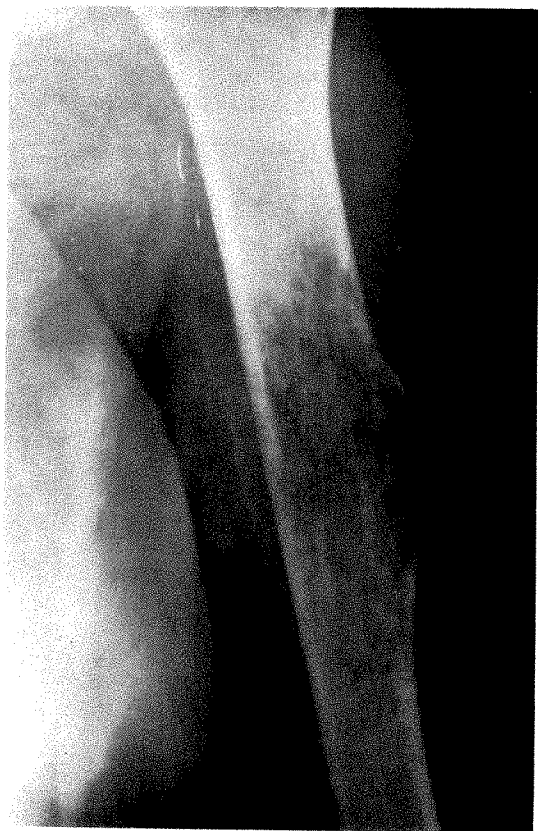


FIG. 2. Case II. Lesion in mid-shaft of left humerus with cortical fragmentation laterally.

and no masses or lymphadenopathy. Skeletal roentgenograms disclosed no other lesions. Open reduction with internal fixation was performed. This was followed by 220 kvp. irradiation. There was no roentgen evidence of healing but the patient remained well for more than six months. She was then re-admitted, having suffered a fracture of the right femur in a fall. Roentgenograms showed this to be pathologic. Open reduction with internal fixation was performed; biopsy revealed reticulum cell sarcoma. No nodes or other masses were found at this time and she was in good general health. However, bone survey revealed several small osteolytic lesions at various sites. A few weeks thereafter she began a rapid downhill course and died three months later. There was no autopsy, but clinical evidence of lymphadenopathy and other soft tissue involvement had appeared prior to death.

CASE III. Female, aged fifty-seven years. This saleslady was admitted with a complaint of bone pain for a period of one year. The pain had its onset in the right hip region, was rather abrupt in onset but not initially severe, and of a fairly constant nature. She was treated symptomatically without real relief. The pain gradually worsened, but not enough to interfere with routine activities. Three months prior to admission there was gradual onset of pain in the left hip also. Two months later, the pain was of such severity that she could no longer work. At that time she began to complain of pain in the right leg. The initial roentgenograms were made at this time and revealed an osteolytic lesion involving the right side of the sacrum from the sacroiliac joint to the mid-line. Another was present in the right acetabular region (Fig. 3), and a third in the proximal right tibia. No other bone lesions were demonstrated. On admission to this institution, a few scattered lytic lesions had appeared in addition to those described, but neither lymphadenopathy nor other soft tissue involvement could be demonstrated. There was early evidence of cord compression due to involvement of a vertebral body with collapse. Needle aspiration and open biopsy of two of the lesions revealed reticulum cell sarcoma. Treatment with roentgen irradiation resulted in moderate recalcification and regression of the lesions. At the present time, one and one-half years after the initial complaint, the bone lesions show further pro-

gression without evidence of soft tissue sarcoma.

CASE IV. Female, aged forty-four. This patient had been complaining of pain in the left leg. The duration of symptoms was uncertain. An osteolytic lesion in the proximal portion of the left tibia was demonstrated roentgenographically. Biopsy revealed a reticulum cell sarcoma of bone. Amputation was performed and a prosthesis fitted. The patient remained asymptomatic for three and one-half years. She then began to complain of pain in the left hip. Roentgenograms showed osteolytic areas distributed throughout the shaft of the left femur (Fig. 4). The remaining bones were found free of disease. She did well for a short while, but the spread could not be controlled and she died of disseminated disease six months after the recurrence.

CASE V. Female, aged eighteen years. This patient initially complained of right posterior

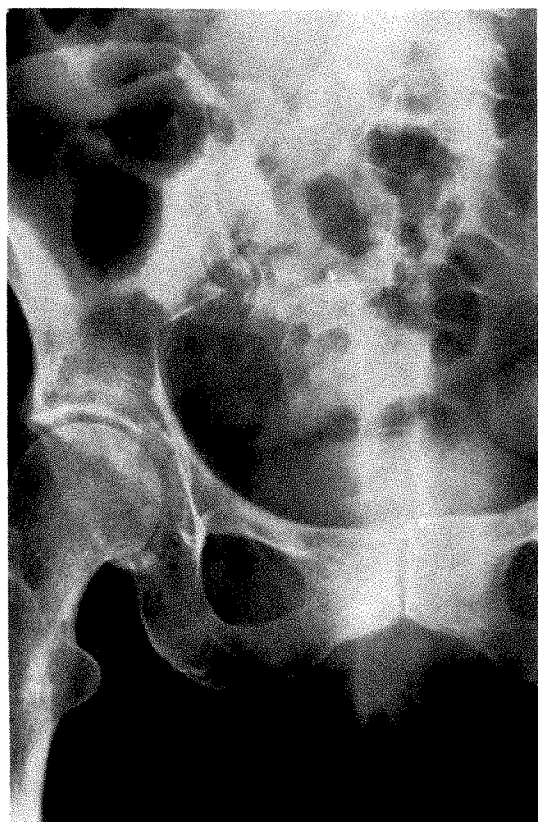


FIG. 3. Case III. Osteolytic lesions in sacrum and ilium. Periosteal reaction is present along the medial aspect of the ilium.

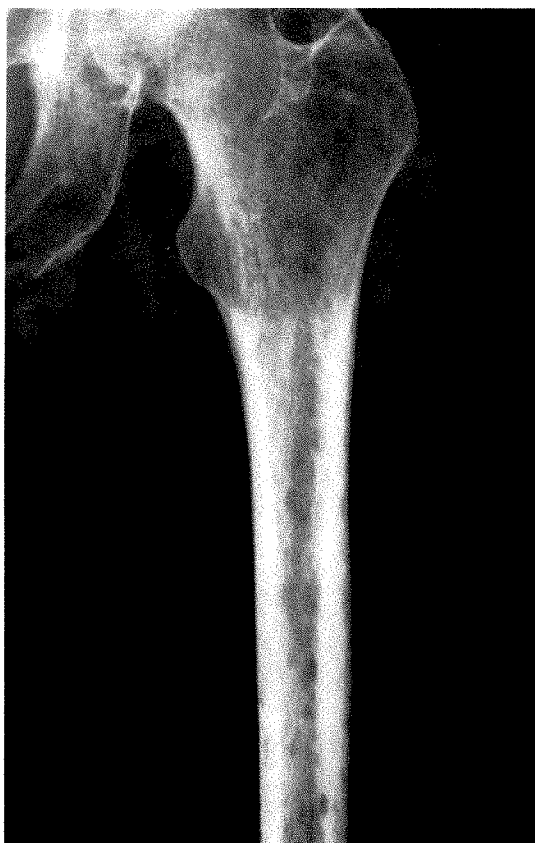


FIG. 4. Case IV. Widespread involvement of left femoral stump three and one-half years following amputation for primary lesion in the tibia.

chest pain of a pleuritic nature which had been present for several months. Six weeks before admission, a slowly growing mass had appeared on the posterior chest. On admission, this was roughly 5 cm. in diameter and seemed to be originating in the ninth right rib. Roentgenograms revealed an osteolytic lesion involving a 5 cm. segment of the ninth rib posteriorly with expansion of the rib and small areas of cortical destruction. The tumor was resected and revealed reticulum cell sarcoma of the rib. Recovery was uneventful, and the patient was discharged without evidence of other involvement. However, recurrence at the operative site supervened four months after the initial surgery. Resection and radiation therapy resulted in temporary improvement, but in a short time anorexia, weight loss, and evidence of dissemination occurred. The patient died about sixteen months after the initial bone lesion was detected.

CASE VI. Female, aged fifty-seven years. This patient's initial complaint was pain in the right shoulder of several months' duration. There had been increasing limitation of motion and, finally, evidence of a pathologic fracture. The roentgen appearance was one of irregular, localized destruction of the head and neck of the humerus, including a small area of cortical destruction and associated with linear periostitis; there was a transverse fracture through the affected area (Fig. 5A). A diagnosis of reticulum cell sarcoma was established by excisional biopsy of a local lymph node mass. The patient was otherwise well, and no other lymphadenopathy was present. Roentgen therapy resulted in relief of symptoms and recalcification of the lesion; the fracture united. The patient was asymptomatic for six months. At this time a deep, boring, but mild pain began in the right leg in the region of the knee joint; a roentgen examination was negative. The pain persisted, and two months later roentgenograms revealed an osteolytic lesion in the proximal tibial shaft with cortical destruction (Fig. 5B). Roentgen therapy resulted in complete healing of the lesion. The patient remained well for two years, when vague left lower quadrant abdominal pain commenced. Roentgenograms showed a 5 cm. osteolytic deposit in the left ilium. Survey of the other bones disclosed no other lesions at that time. The patient then began to show evidence of debilitation and subsequently died, more than three and one-half years after the initial lesion was discovered.

CASE VII. Female, aged ten years. A painful swelling in the right axillary region was the initial complaint. The duration was uncertain. This was clinically associated with, and thought to be arising from, the rib cage. Roentgen examination revealed an 8 cm. lesion involving the right fourth rib in the mid-axillary line (Fig. 5C). It was characterized by osteolytic and osteoblastic areas, bone expansion, and small areas of cortical destruction. This was resected and found to be reticulum cell sarcoma. Cobalt 60 teletherapy was administered to the area following surgery. The patient is alive with no evidence of recurrence six and one-half years after the initial symptoms.

CASE VIII. Female, aged forty years. This patient was admitted with severe pain in the left groin of sudden onset, without antecedent trauma. She was otherwise in good health.

Roentgenograms revealed an irregular osteolytic lesion involving a 5 cm. length of the left superior pubic ramus (Fig. 5D). A pathologic fracture was present. The cortex was expanded but not destroyed, and the junction of normal and abnormal bone was ragged and ill-defined. There was a history of carcinoma of the thyroid four years previously, completely excised and without evidence of recurrence or dissemination. The pubic lesion was explored, and as much as possible of the tumor was removed. The pathologic diagnosis was reticulum cell sarcoma of bone; it was further stated that it was definitely not related to the previous thyroid carcinoma. No other lesions could be demonstrated, and the patient was otherwise well. Cobalt 60 teletherapy was undertaken. Despite relief of pain, healing of the lesion was incomplete. The patient remained asymptomatic for approximately four months. Pain then began in the right thigh, and further mottled localized bone lesions were demonstrated in the right femur and skull. Despite the absence of other demonstrable lesions, the patient suddenly began to deteriorate, and died about six months after the initial lesion was demonstrated. Autopsy confirmed the diagnosis. Many small lesions were found in the soft tissues as well as the bones.

COMMENT

Only one male is included in this group; 3 of the patients were forty years or less in age. All were white. The single long term survival had a primary lesion in rib, as did one of the other patients; 4 lesions originated in long bones, and 2 in the pelvis. The histologic diagnosis was reached by at least two pathologists in all instances; cases in which there was any disagreement were discarded.

The roentgenologic picture is in no way different from the previous descriptions^{2,15} of circumscribed but poorly margined mottled or osteolytic bone involvement, apparently originating in the medullary cavity. The tumor may occur at any site in the bone affected. Cortical destruction is generally present, though neither bone expansion nor periosteal new bone formation is a feature of the lesion. In those cases with demonstrable cortical destruction, an appreciable soft tissue mass may occasionally

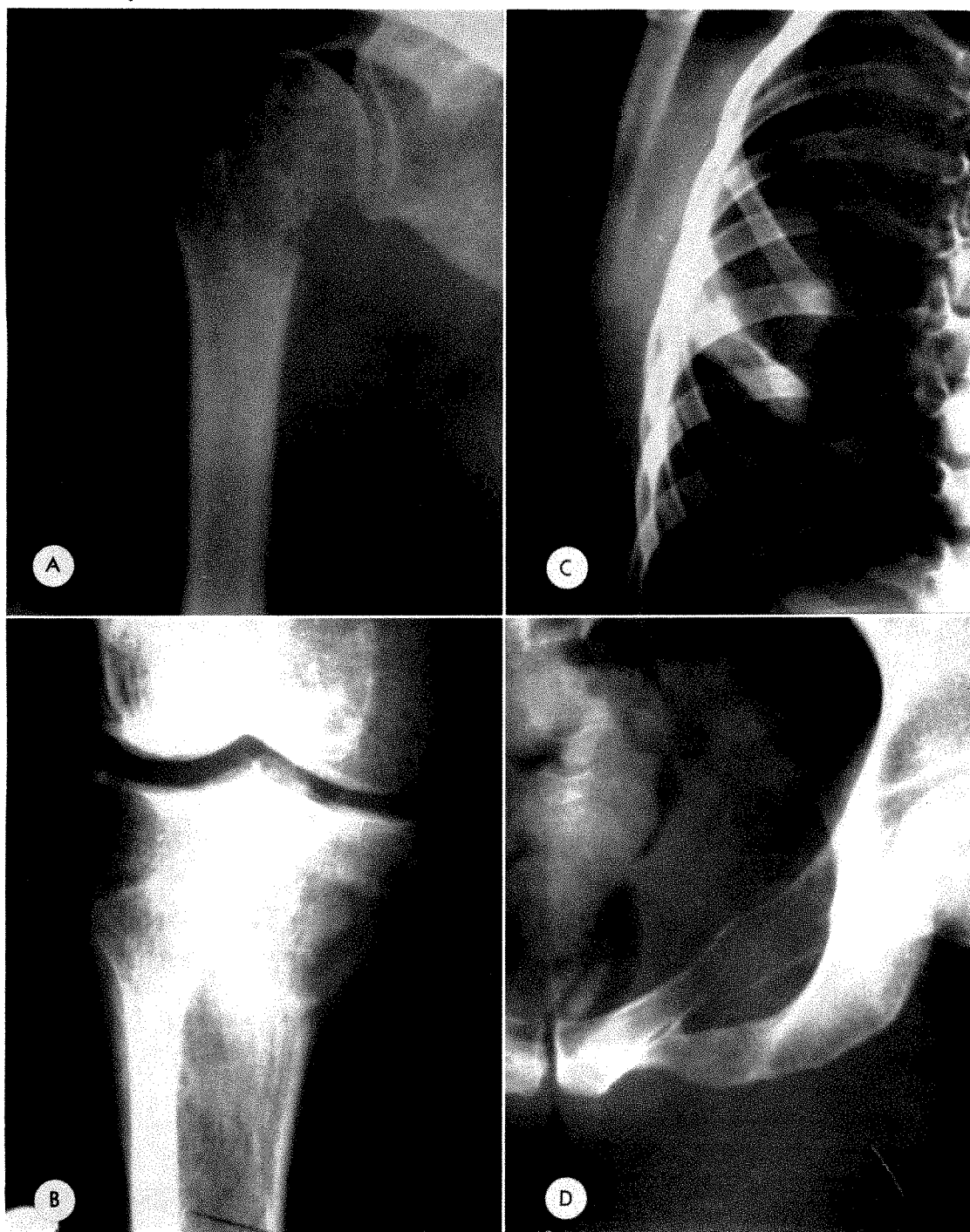


FIG. 5. (A) CASE VI. Mottled lesion in proximal humerus with cortical destruction and fracture of the neck. (B) Case VI. Right tibial metastasis from reticulum cell sarcoma in the right humerus. (C) Case VII. Lesion apparently arising in right fourth rib, with an associated large soft tissue component. (D) Case VIII. Destructive, mildly expansile lesion originating in pubic ramus.

be associated. The periosteal component is not characteristic. The manifestations of recurrent disease in Case IV are somewhat unusual in that the destruction in the femur showed innumerable small lytic lesions of varying size, somewhat ill-defined and lacking clarity. However, as has been recently stated "...reticulum cell sarcoma... is often characterized by bizarre metastases."¹³

DISCUSSION

The criteria for diagnosis of primary reticulum cell sarcoma of bone are usually stated^{2,14} as:

1. The primary focus should originate in a single bone.
2. The biopsy material should be obtained from the bone lesion.
3. The histologic pattern should be that of reticulum cell sarcoma.
4. There should be a long natural history without generalized symptoms.
5. The metastatic lesions should be limited to the regional lymph nodes, or not make their appearance within six months of the primary.
6. The neoplasm should be highly radiosensitive.

At least some of these criteria appear to be unduly rigid. That it should be identified by a competent pathologist as reticulum cell sarcoma and that the original manifestation should be in bone cannot be denied. The other criteria are not so easily defended and have, to a certain extent, been tacitly criticized or ignored by other authors.^{6,8} Stringent application will certainly ensure that the lesions discussed include only primary reticulum cell sarcoma of bone. However, the danger exists that this approach may exclude cases in which the course is somewhat different; that is, a group may be selected, the behavior of which is more benign than that of reticulum cell sarcomas of bone as a whole. With these rigid criteria the five year survival rate with irradiation, surgery, or some combination of the two, is in the neighborhood of 35 per cent.⁶ The most that

can be said is that this is somewhat better than occurs with most other primary malignant tumors of bone. In addition, the final picture in the patients succumbing to their lesion is one of generalized disease. If the criteria were realistically relaxed to demand only that the histologically characteristic lesion be initially restricted to bone with or without regional lymph node involvement, it is probable that the resultant alteration in long term survival would considerably temper the optimism with which the lesion is sometimes viewed. This, of course, is not to say that localized reticulum cell sarcoma with a favorable clinical history is not to be viewed hopefully. It is suggested, however, that reticulum cell sarcoma originating in bone has a spectrum of behavior ranging from highly malignant and rapidly fatal to relatively benign and curable.

When considering the localized lesions of the lymphosarcomas in bone, it is probably worthwhile to contemplate the behavior of localized lymphosarcomas arising in soft tissues. These latter compare in rarity to the local lesions of bone, and large series with statistical validity are difficult to find. However, there are increasing numbers of such cases being reported, and the localized soft tissue lesion appears to compare favorably with the localized bone lesion. In other words, reticulum cell sarcoma of bone is not fundamentally different from reticulum cell sarcoma of soft tissues; in either case the patient with a localized lesion and a long antecedent history has a more hopeful outlook than otherwise. This is true of the breast,⁵ the small bowel,⁷ maxillary antrum¹⁸ and stomach.^{16,17} If the impression of Ackerman and del Regato¹ is correct that there are increasing numbers of localized soft tissue lymphosarcomas being discovered (presumably due to factors contributing to earlier diagnosis), more evidence may eventually be adduced to prove or disprove this view.

CONCLUSION

From the 8 cases of reticulum cell sar-

coma of bone presented and a consideration of studies published by others, it is felt that a diagnosis of primary reticulum cell sarcoma of bone should not be subject to the rigid criteria applied in the past. Though the lesion is, in general, more benign than most primary malignant bone tumors, it does not have as favorable a prognosis as is often thought. Its behavior is probably not significantly different from that of the solitary reticulum cell sarcoma arising elsewhere.

SUMMARY

1. Eight cases of reticulum cell sarcoma apparently originating in bone are presented.

2. The behavior of these lesions in relation to other localized lymphomata is briefly discussed.

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I wish to acknowledge my indebtedness to Dr. Peter C. Conlon of Pittsburgh, Pennsylvania, for many fruitful discussions of the ideas expressed above.

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MEDICAL SCINTILLATION SCANNING UTILIZING CLOSED CIRCUIT TV CONTRAST ENHANCEMENT*

TECHNICAL ASPECTS

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MEDICAL scintillation scanning began in 1950 with the development by Cassen and associates⁸ of an instrument capable of measuring the spatial distribution of radioactive iodine in the human thyroid gland. Following this report, innumerable developments ensued in the medical applications of scintillation scanning. Brownell and Sweet⁷ utilized positron-emitting isotopes for brain tumor localization. Friedell *et al.*¹¹ developed a technique for liver scanning and MacIntyre and Houser¹⁸ introduced the concept of count rate cut-off in order to increase contrast on the dot recorder. A notable advance in data presentation was made when Horwitz and Lofstrom¹³ introduced photorecording and Kuhl *et al.*¹⁴ further refined the technique.

The distribution of radioactivity in an organ had previously been represented by dots on paper. Now, with photo recording radioactivity distribution was revealed by changes in film density from gray to black. The change from gray to black on the photographic film was a function of count rate and gave each dot a count rate value. Potentially, one could recognize subtle changes in the distribution of radioactivity; however, the ability of the human eye to resolve the varying shades of gray had been exceeded.

In 1959, Bender and Blau² overcame the difficulty of recognizing small changes in film density by utilizing closed circuit tele-

vision to effect an infinitely variable electronic background erase and contrast enhancement. Here, the scanner was adjusted to record all radiation pulses with low contrast on the photographic film. The film was then viewed by means of closed circuit television. Background erase and contrast enhancement were effected electronically. With this technique all information was recorded and became interpretable. Few repeat scans were required because of improper technical adjustment of the photoscanner and with this method radioactivity differences of as little as 5 per cent could be detected. By overriding the contrast control on the television camera, successive count rates may be viewed which, in effect, act as "count rate planography." The organ can be viewed at successive count rates and tumors detected in depth.

Various scanners have been built or modified by medical teaching centers. Reports of techniques for organ scanning are scattered throughout the recent medical literature. We wish to present our synthesis of medical photoscanning, utilizing unmodified commercial equipment. Sufficient technical detail is given to enable one to readily obtain scans of a high degree of quality. This paper will not attempt an assessment of diagnostic accuracy; however, the quality of the scans indicates that accuracy of this technique will equal or exceed that of reported series.^{16,20}

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MATERIALS

A Picker* magnascanner #2806, equipped with a 3"×2" thallium-activated sodium iodide scintillation probe (model 2809-A) was utilized throughout. Basic operation of the scanner was in accordance with instructions contained in Picker* manuals T55-260 and T55-222. Our modifications of technique are noted under the respective organ sections. Herring¹² has recently published a detailed electronic discussion of this photoscanner. The pulse height analyzer was calibrated with Cs¹³⁷ from 0 to 1 mev. A Ling† spectator closed circuit television system (camera model V1051) and video-monitor (model FP-0001) were utilized unmodified. The camera and monitor were mounted as illustrated in Figure 1. A high-intensity, fluorescent light viewbox was used as a light source in the closed circuit system for viewing the scans. By adjusting the brightness and contrast controls of the television camera, successive count rates may be viewed on the monitor screen. With the television monitor picture properly adjusted, photographs were made with a Polaroid‡ Land camera (model 800). Polapan 200-type 42‡ film was found to be suitable for photographing the monitor screen image. Copies of the photographed scans were kept in departmental records and a copy, with interpretation, was sent to the referring physician. Immobilization of the head or body was carried out with a dilatancy bag (Flexicast-Picker*).

COLLIMATION

A Picker* fine focus, 31 hole collimator (model 2102) was utilized in thyroid scanning with a 1 mm. dot light shaper. The Picker* coarse focus, 19 hole collimator (model 2107) was used with a 3×3 mm. square light shaper for scanning all organs except the thyroid gland.

* Picker X-ray Corp., The Waite Mfg. Div., Inc., Cleveland, Ohio.

† The Ling Electronic Co., P.O. Box 5570, Dallas, Texas.

‡ Polaroid Corporation, Cambridge 39, Massachusetts.

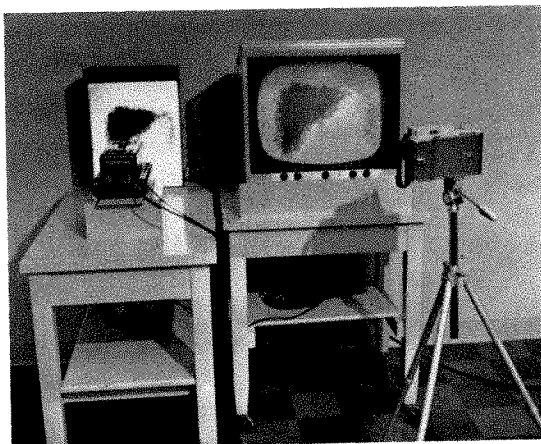


FIG. 1. Photograph illustrating the closed circuit television setup of the Radioisotope Laboratory, National Naval Medical Center. The television camera mount is capable of vertical and horizontal movement to facilitate scan viewing.

PHOTOSCANNING CONTROLS

The photo recording controls of the magnascanner are three in number: the high voltage adjustment, the density control, and the count per minute range differential.

The high voltage adjustment controls the voltage applied to the cathode-ray light source of the photo recorder. This voltage value is supplied with each scanner.

The density control is the switch which controls the duration in microseconds of each light flash in the photo recorder. The proper duration of each light pulse is a function of scan speed and the average maximum count rate. Table 1 gives the relationship of density setting to maximum count rate and scan speed when utilizing the 3×3 mm. square light shaper.

The count per minute (CPM) range differential is a contrast enhancement control. This allows one to vary film density over a given count range. Figure 2 illustrates the variations in slope of the film density curve obtained with high and low count per minute range differential settings when the density control values are held constant. Low count per minute range differential settings give high contrast scans

TABLE I
DENSITY CONTROL SETTING IN MICROSECONDS
FOR 2.0 DENSITY

Average Maximum CPM	Scan Speed in Centimeters per Second					
	60	50	40	30	20	10
10,000	25	25	18	18	12	8
5,000	50	50	25	25	18	12
2,000	100	100	50	50	50	50
1,000	—	—	—	100	100	50

Blue Brand Film, 4.5 minutes developing time at 68°C.

but blindly sacrifice scan information. High count per minute range differential settings give low contrast scans but record all information on the film. One may then effect proper contrast enhancement through closed circuit television. No information is lost and the contrast enhancement is variable and reversible.

BRAIN SCANNING

TECHNICAL DETAILS

The isotope employed is neohydrin Hg^{203} (Abbott Laboratories*) at a dose rate of 4 $\mu\text{C}/\text{kg}$., given intravenously.

The pulse height analyzer of the photo-scanner is adjusted to count 0.28 mev. gamma emission of Hg^{203} centered in an 80 kev. window. The rate meter time constant is set at $\frac{1}{3}$ th second on a scale of 1K with a count per minute range differential setting of 50 per cent. The average maximum count rate over the cheek is 500 CPM and the scanning speed averages 20 cm./min. Film density settings are obtained from Table I. Scans are made in the anteroposterior and lateral positions with a total elapsed time for scanning approximately one and one-half hours.

DISCUSSION

There is no preparation of the patient for the scan. On the morning of the scan, the patient is given the appropriate dose of Hg^{203} neohydrin, intravenously, and at

* Abbott Laboratories, Oak Ridge, Tennessee.

least one hour is allowed to elapse for mixing and for fixing of the isotope if a lesion exists. Approximately fifty minutes post injection, the patient is carefully positioned beneath the probe and the photo-scanner properly adjusted. The count rate over the cheek is used as the maximum count rate. The head is immobilized by the Picker-Flexicast bag and the probe is adjusted to pass as closely as possible to the head, generally within one-half inch. In the lateral projection landmarks are placed at the base of the nose, the external canthus of the eye, and at the external auditory canal, the occiput and the vertex. In the anteroposterior projection landmarks are placed at the base of the nose, the middle of each orbital ridge and at the vertex of the skull. Appropriate markers are placed to indicate right and left on the scan. Figures 3, *A* and *B* and 4, *A*, *B* and *C* are illustrative of typical brain scans.

Neohydrin tagged with radioactive mercury 203 is the compound of choice for brain scanning.⁴ The long half-life of 47.9 days allows one to keep the isotope in stock without undue loss from radioactive decay, and Hg^{203} neohydrin can also be used for kidney scans. McAfee and Wagner¹⁷ reported an average effective half-life of three hours for Hg^{203} neohydrin. More re-

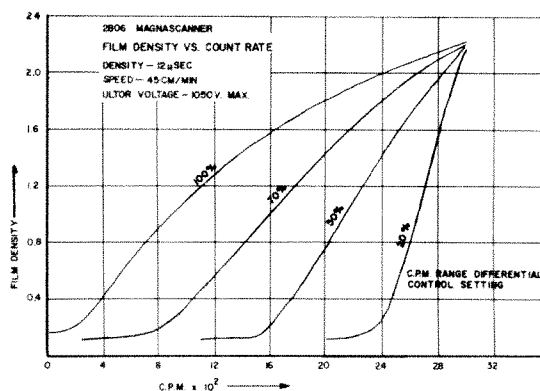


FIG. 2. Graph illustrating the effect of count per minute range differential settings on the slope of the film density curve when the density control is held constant. Steep film density curves give high contrast scans, whereas a flat slope yields a low contrast scan.

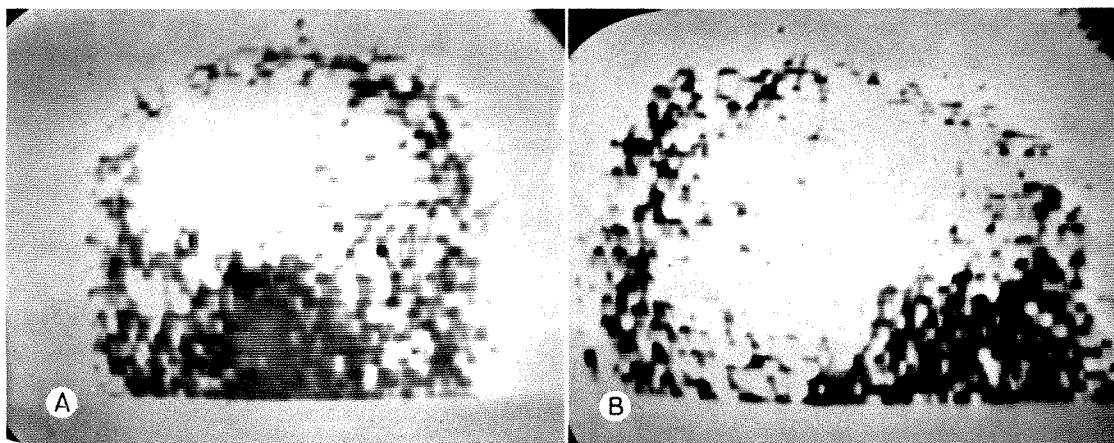


FIG. 3. (A) Photograph of TV monitor screen image of a normal anteroposterior photoscan of the brain done 1 hour post dose of $4 \mu\text{c/kg.}$ of Hg^{203} neohydrin. (B) Photograph of TV monitor screen image of a normal left lateral photoscan of the brain at 1.5 hours post $4 \mu\text{c/kg.}$ of Hg^{203} neohydrin.

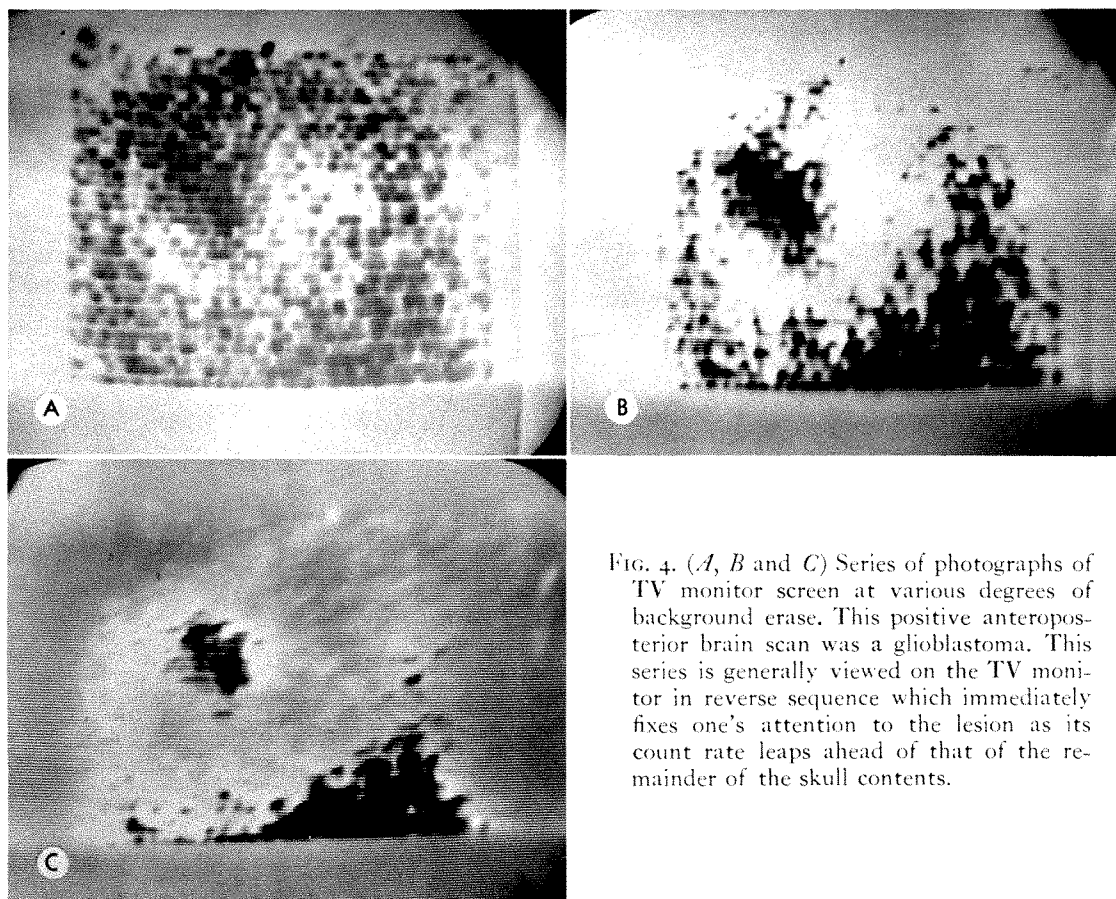


FIG. 4. (A, B and C) Series of photographs of TV monitor screen at various degrees of background erase. This positive anteroposterior brain scan was a glioblastoma. This series is generally viewed on the TV monitor in reverse sequence which immediately fixes one's attention to the lesion as its count rate leaps ahead of that of the remainder of the skull contents.

cent experience indicates that approximately 10 per cent of the administered dose of Hg^{203} neohydrin remains fixed to renal parenchyma with an effective half-life of 18 days. This renal binding of the neohydrin may be blocked by giving 1 cc. of mercurhydrin* intramuscularly the day prior to scanning;⁵ however, it is not clear what effect this premedication may have on tumor binding of the Hg^{203} neohydrin. Utilizing 4 $\mu\text{c}/\text{kg}$. Hg^{203} neohydrin and correcting for 10 per cent retention in the critical organ, the kidney, one may estimate the total body dose at 0.006 rads and the individual kidney dose at 18.27 rads. This laboratory does not employ a blocking dose of mercurhydrin because the effect of this drug on tumor localization is not known, the kidney exposure is not unreasonable, and premedication imposes a delay in scanning. The physical radiation emission of Hg^{203} is also advantageous. The single 0.28 mev. gamma emission is ideal for collimation purposes. In contrast, I^{131} has two gamma emissions of 0.64 and 0.72 mev. and a third major emission of 0.36 mev. The higher mev. gamma emissions of I^{131} are difficult to collimate. Another advantage of the use of Hg^{203} neohydrin is found in the rapidity with which a scan may be obtained. Excellent localization is observed in as little as one hour post injection, whereas the waiting period for I^{131} human serum albumin is at least twenty-four hours.

Iodine¹³¹ human serum albumin may also be employed for brain scanning.^{9,16} Ten drops of Lugol's solution must be administered at least the day before this isotope is given and for four days following the injection of the scanning dose. This will effectively block the thyroid uptake of the radioactive iodine. On the day before the scan is to be done, 5 $\mu\text{c}/\text{kg}$. of I^{131} human serum albumin is administered intravenously. Twenty-four to thirty-six hours later, the scan is carried out as has

been outlined above for the use of Hg^{203} neohydrin. In this case, the pulse height analyzer is adjusted to count the 0.36 mev. gamma emission of I^{131} centered in an 80 kev. window. Count rates and scanning time are approximately the same for the use of this isotope. The primary disadvantage in the use of iodinated human serum albumin is in the delay necessary for the obtaining of adequate scans. Of course, the relatively short half-life of I^{131} also necessitates frequent ordering of the isotope and unless the thyroid has been properly blocked by the use of Lugol's solution, there is a danger of I^{131} uptake by the gland and damage to this organ. Utilizing Sterling's¹⁹ data on I^{131} albumin metabolism in normals whose thyroids had been blocked with Lugol's solution, the whole-body dose is approximately 0.5 rad. Excellent and extensive discussions on the use of I^{131} human serum albumin for brain scanning have been published by McAfee and Taxdal¹⁶ and Di Chiro.⁹ The latter author recommends a three day preparation of the patient with Lugol's solution thus imposing a further delay in obtaining a scan. Finally, we would like to emphasize the use of brain scanning as a valuable means of screening psychiatric patients. Regardless of the isotope chosen, brain scans are an excellent atraumatic means of detecting intracranial tumors.^{9,16}

THYROID SCANNING

TECHNICAL DETAILS

The isotope employed is iodine¹³¹ (Iodotope, Squibb†). The adult dose is 25 μc administered orally.

The pulse height analyzer is set to count the major gamma emission of I^{131} of 0.36 mev. centered in an 80 kev. window. The rate meter time constant is $\frac{1}{8}$ th second with a scale of 3K. The count per minute range differential is 80 per cent of the average maximum count rate of 1,000 CPM. Scanning speed is 30 cm./min. with film density

* Mercurhydrin Sodium, Lakeside Laboratories, Inc., Milwaukee, Wisconsin.

† E. R. Squibb and Sons, Squibb Road, King of Prussia, Pennsylvania.

settings obtained from Table 1. Note that here, for greater detail, the 31 hole, fine focus, Picker collimator is employed, utilizing a 1 mm. dot light shaper and line spacing of 0.2 cm. Scans are made in the anteroposterior projection with average scanning time of approximately thirty minutes. Landmarks are placed at the suprasternal notch, the cricoid cartilage and the right and left side of the neck.

DISCUSSION

Figure 5*A* shows the print-out obtained from the usual dot recorder. Note that the detail of the "cold" thyroid nodule is not well presented. Figure 5*B* is a photscan of the same gland. A marker has been placed over the "cold" nodule which has been well outlined. At the base of the left thyroid lobe, it is noted that there is a "cold" area with a "hot spot" in the center. This detail was not appreciated in the printed write-out. At operation, benign bilateral cysts of the thyroid were found.

Indications for thyroid scanning are well known; however, it should be pointed out that low contrast scans have proven useful as a postoperative parameter for assessing the thoroughness of surgery. Frequently, metastases and small bits of overlooked

thyroid tissue may be visualized. The dose to the thyroid gland, based on a normal uptake of I^{131} , is approximately 35 rads. The total body dose is in the range of 50 millirads.

HEART AND GREAT VESSEL SCANNING

TECHNICAL DETAILS

It is necessary to premedicate the patient with Lugol's solution, 10 drops per day, on the day before and four days post scan dose. Iodine¹³¹ labeled human serum albumin (Albumotope, Squibb) is the isotope employed. A dose of 5 μ c/kg. is given intravenously, at least thirty minutes before scanning.

The pulse height analyzer is set to count the primary gamma emission at 0.36 mev. centered in an 80 kev. window. The rate meter time constant is $\frac{1}{8}$ th second with a scale of 10K. The count per minute range differential is adjusted to count 15 per cent of the average count rate over the precordium which is 3,800 to 4,000 CPM. The average count rate over the lungs is 1,500 CPM. Scanning speed is 30 cm./min. and film density settings are obtained from Table 1. The scan is obtained in the anteroposterior projection with an average of thirty minutes scanning time. Landmarks

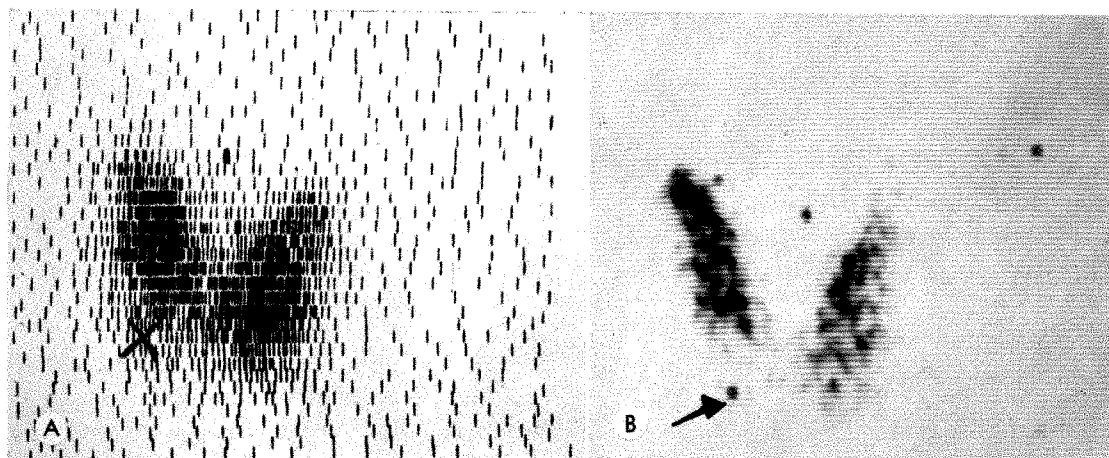


FIG. 5. (*A*) Conventional dot recording of a thyroid scan. X indicates location of a palpable nodule. Note that the left lobe of the gland appears to be within normal limits. (*B*) Photscan of same thyroid illustrated in *A*. A marker has been placed over nodule at arrow. Note here that the base of the left lobe of the thyroid has an unsuspected "hot spot" surrounded by a "cold area." At operation, bilateral benign cysts of the thyroid were found.

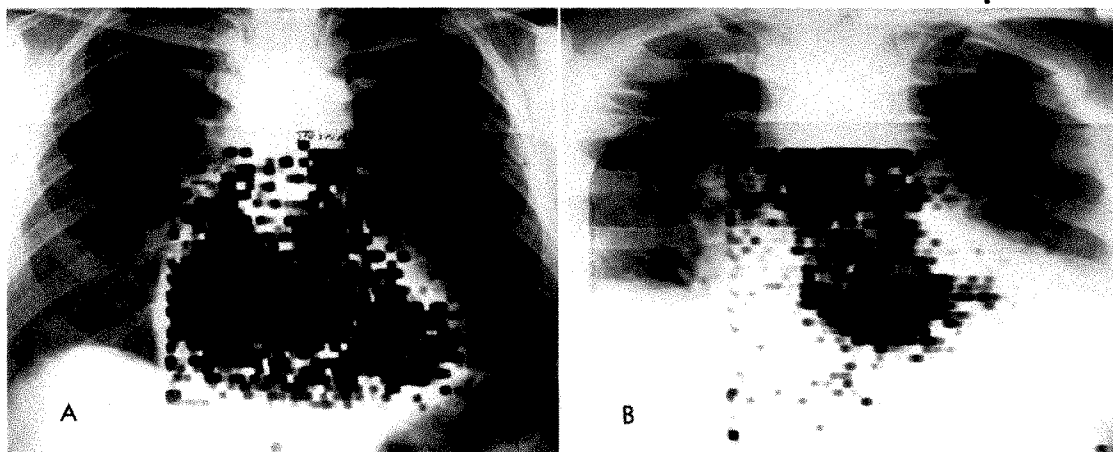


FIG. 6. (A) Photoscan of heart superimposed on chest roentgenogram. The large heart shadow is completely filled with darkened film which represents the distribution of I^{131} RISA in the heart's chambers. Anatomic diagnosis was cardiomegaly secondary to congenital interventricular septal defect. (B) Photoscan of heart superimposed on chest roentgenogram. The large heart shadow contrasts vividly with the darkened film which represents ventricular size. Anatomic diagnosis was pericardial effusion secondary to Hodgkin's disease.

are placed at the sternal notch, the xiphoid and the left and right of the chest. A standard chest roentgenogram with lead markers placed in the above locations is obtained and the scan and chest roentgenogram are superimposed (Figure 6, A and B).

DISCUSSION

Scanning of the heart and great vessels has proven of value in distinguishing blood containing masses located within the chest or abdomen. Its usefulness in differentiating cardiomegaly from pericardial effusion has recently been evaluated.²¹ The radiation exposure from this procedure is estimated at 0.5 rad whole-body radiation. If the thyroid gland has been properly blocked with Lugol's solution, the dose to the thyroid gland is the same as the whole-body dose.

LIVER SCANNING

TECHNICAL DETAILS

No premedication or special procedures are necessary prior to scanning the liver. The isotope employed is colloidal gold 198 (Aureotope, Squibb). The dose is 1.5 μ c/kg., given intravenously at least one

hour before scanning, and a maximum dose of 100 μ c Au^{198} is observed. The Au^{198} is routinely discarded by this laboratory after three half-lives and replaced with fresh isotope.

The pulse height analyzer is adjusted to count the 0.411 mev. gamma emission of Au^{198} with an 80 kev. window. The rate meter time constant is $\frac{1}{8}$ th second with a scale of 3K. The count per minute range differential is set at 50 per cent of the average maximum count rate of 2,000 CPM. Scanning speed is 30 cm./min. and film density settings are obtained from Table 1.

The patient is carefully placed under the scanner at least one hour post dose and the probe adjusted to pass one-half inch from the skin. The probe should traverse the entire upper abdomen, particularly to cover the splenic area. The average scanning time is approximately one hour. Landmarks are placed at the xiphoid, the right lower rib margin, and the right and left of the scan are indicated. A standard flat film of the abdomen, with lead markers placed on the xiphoid and the right lower rib margin, can be obtained for superimposition on the scan. The radiation dose to the liver at this dose level of Au^{198} is approximately 5 rads.

DISCUSSION

The usefulness of scanning of the liver has been well documented recently in a paper by Wagner and colleagues.²⁰ Usefulness of liver scans in the differential diagnosis of right upper quadrant masses has been well demonstrated. Its value has been emphasized in metastatic disease to the liver, differential diagnosis of abdominal masses, the differentiation of obstructive parenchymatous liver disease, and the preoperative evaluation of patients with malignancies. Closed circuit TV has proven most useful in evaluating liver scans (Fig. 7, *A*, *B* and *C*).

Several helpful diagnostic signs have been noted in liver scanning. Since the colloidal gold is picked up by the reticulo-

endothelial system of the liver, when this system has been depressed, such as in infectious hepatitis or in cirrhosis of the liver, the reticuloendothelial system of the spleen is able to compete favorably for the uptake of the gold. Therefore, when significant splenic uptake is present, one should suspect depression of the reticuloendothelial system of the liver and parenchymatous liver disease.

Recently, reports have become available from Sweden¹⁵ which show that in myeloproliferative disorders there is considerable uptake of the radioactive gold by the bone marrow, particularly the vertebral marrow. When uptake of the Au¹⁹⁸ is observed in this tissue, as illustrated in Figure 8, it should be called to the attention of the con-

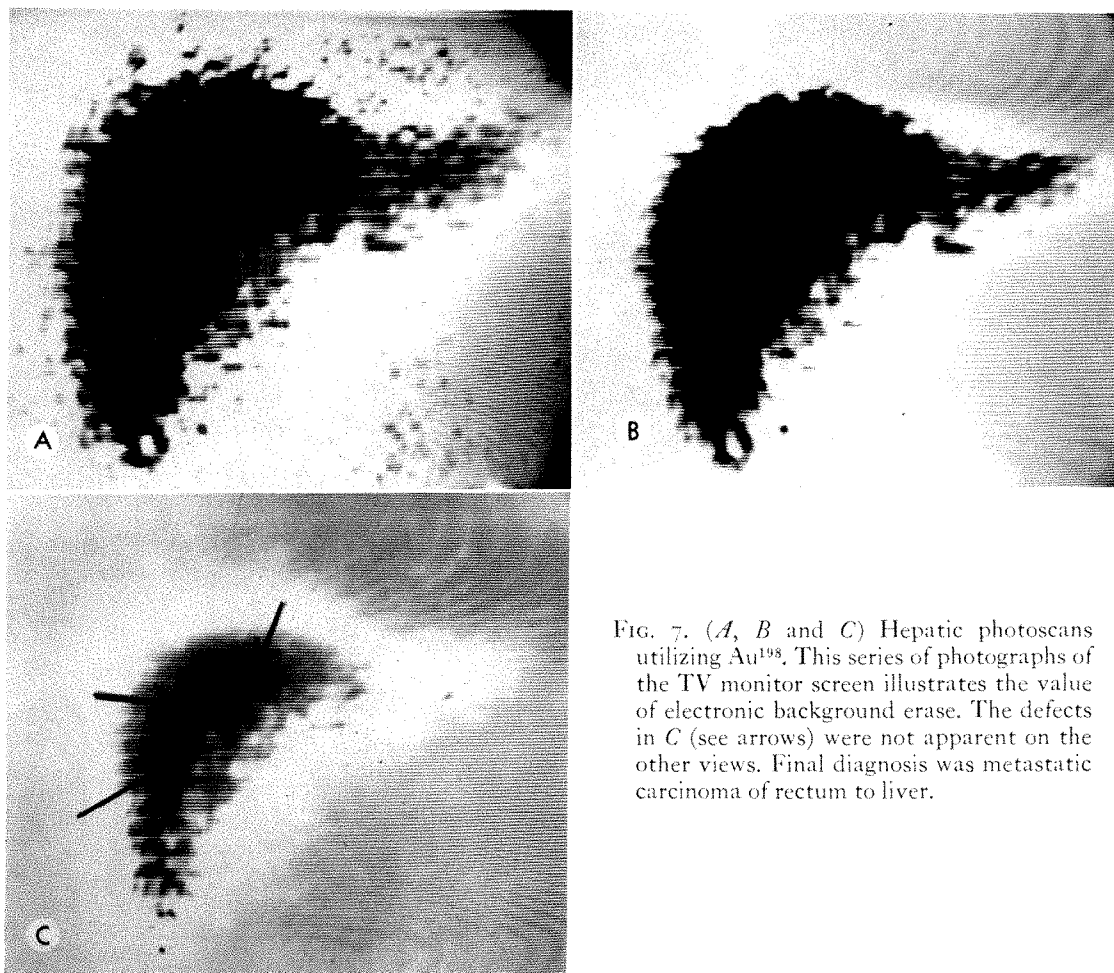


FIG. 7. (*A*, *B* and *C*) Hepatic photoscans utilizing Au¹⁹⁸. This series of photographs of the TV monitor screen illustrates the value of electronic background erase. The defects in *C* (see arrows) were not apparent on the other views. Final diagnosis was metastatic carcinoma of rectum to liver.

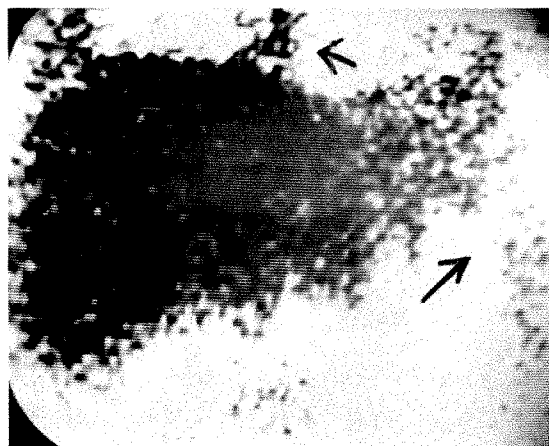


FIG. 8. Photostatic of liver utilizing Au^{198} . Note pickup of isotope in vertebral marrow and spleen (arrows). Bone marrow aspiration revealed plasma cell leukemia.

sulting physician, and bone marrow evaluation should be undertaken.

I^{131} rose bengal has been utilized for liver scanning³ but has a number of disadvantages and scan quality is poor. When utilizing this isotope, one must employ a loading dose of rose bengal to prevent rapid excretion from the liver. It should be remembered that the concentration of I^{131} rose bengal in the liver varies considerably during the scan.

SPLEEN SCANNING

TECHNICAL DETAILS

The isotope employed is hexavalent chromium 51 (Chromitope, Squibb) at a dose level of 200 μc for an adult. No premedication is indicated.

The technique of Winkelman *et al.*²² is utilized unmodified. The morning of the scan 10 ml. of the patient's blood is withdrawn into a sterile syringe containing 2 ml. of ACD anti-coagulant solution. Two hundred microcuries of hexavalent Cr^{51} are added and incubated with the blood at room temperature (22°C .) for fifteen minutes. After incubation, 50 mg. of ascorbic acid is added to reduce the residual chromate ions and terminate tagging. The blood chromate solution is then incubated

in a water bath at $49.5^\circ\text{C} \pm 1^\circ$, for one hour to produce crenation of the red cells. The blood is cooled to room temperature and reinjected intravenously into the patient. It is necessary to inspect for hemolysis prior to injection and not inject if visible hemolysis has occurred. The patient is scanned at one hour post dose although one may wait longer before scanning.

The pulse height analyzer is adjusted to count 0.323 mev. gamma emission of Cr^{51} centered in an 80 kev. window. Rate meter time constant is $\frac{1}{8}$ th second with a scale of 1K. The count per minute range differential is set at 40 per cent of an average splenic count rate of 500 to 600 CPM. Scanning speed is 30 cm./min. Film density settings are obtained from Table 1. Scanning time is a little less than one hour. Landmarks are placed at the xiphoid and the left lower rib margin. A standard flat film of the area is taken with lead markers at the same position, and the scan and film are superimposed.

DISCUSSION

It should be noted that high contrast scans with very low count per minute range differential settings are deceptive when scanning this organ. Because of its shape, the spleen when scanned with high contrast gives one a false impression of smallness. This is illustrated in Figure 9, A, B and C. Spleen scanning has proven useful in defining left upper quadrant masses, the degree of splenomegaly, splenic infarct location, the location of functioning splenic tissue and accessory spleens. Radiation dose to the spleen is approximately 4 rads at this dose level of chromium 51. The effective half-life in the splenic area is approximately eight days. The total-body dose in this technique is less than 0.05 rad.

KIDNEY SCANNING

TECHNICAL DETAILS

No premedication is indicated. The isotope employed is Hg^{203} neohydrin (Abbott Laboratories) at a dose level of 1.5 $\mu\text{c}/\text{kg}$. given intravenously. A maximum dose of

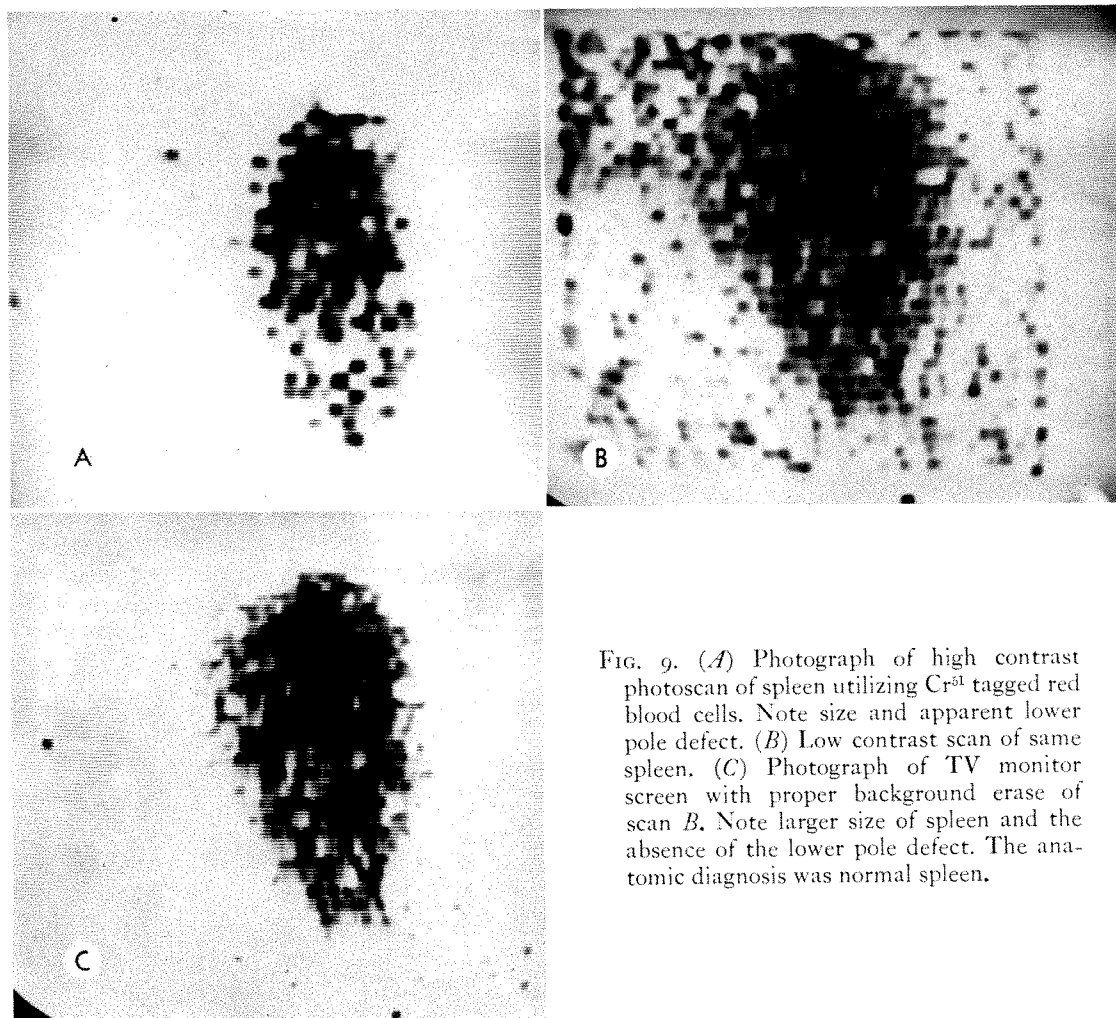


FIG. 9. (A) Photograph of high contrast photoscan of spleen utilizing Cr^{51} tagged red blood cells. Note size and apparent lower pole defect. (B) Low contrast scan of same spleen. (C) Photograph of TV monitor screen with proper background erase of scan B. Note larger size of spleen and the absence of the lower pole defect. The anatomic diagnosis was normal spleen.

50 μc is observed.

The pulse height analyzer is set to count the 0.28 mev. gamma centered in an 80 kev. window. Rate meter time constant is $\frac{1}{8}$ th second with a scale of 3K. The count per minute range differential is set at 20 per cent of the average maximum count rate over the kidney region of approximately 2,000 CPM. Scanning speed is 30 cm./min. Film density settings are obtained from Table 1. The patient is scanned in the prone position and landmarks are placed over the spine at T1 and S1, and at the left and right lower rib margins. Lead markers are placed over the same areas and a flat film is taken of the abdomen. The scan and film are then superimposed (Fig. 10).

Scanning time is approximately fifty minutes.

DISCUSSION

This technique has proven useful for localizing the kidneys when the intravenous pyelogram has failed to show excretion, and particularly useful in the evaluation of left upper quadrant and right upper quadrant masses.¹⁷ Renal tumors, polycystic renal disease and renal infarcts can be demonstrated. Scans may be repeated at twenty-four hours to gain an impression of calyceal structure. The radiation dose delivered to the kidney has been estimated at approximately 3.25 rads with a total-body dose of 0.001 rad.

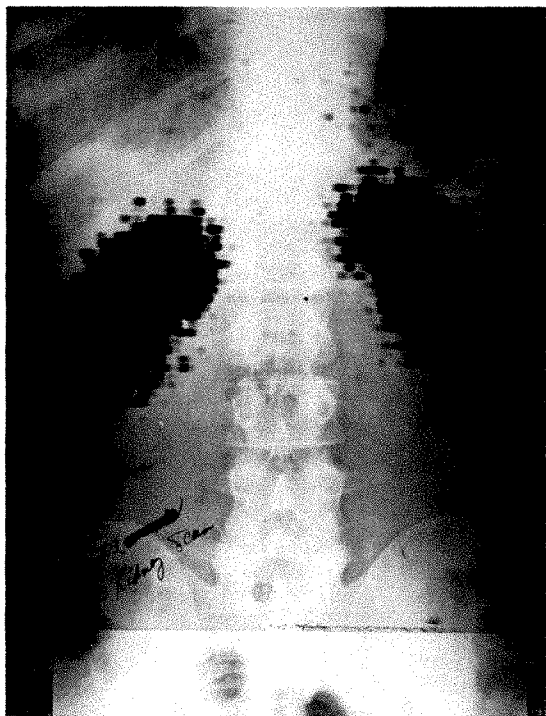


FIG. 10. Normal kidney photoscan superimposed on flat film of abdomen. Scan done 1 hour post 50 μ c of Hg^{203} neohydrin.

BONE SCANNING

TECHNICAL DETAILS

The preferred isotope is strontium 85 obtainable from Oak Ridge National Laboratories, Oak Ridge, Tennessee. A stock solution is prepared by first neutralizing the strontium 85 which is delivered dissolved in acid, and then diluting in physiologic saline to a concentration of 20 μ c/ml. This solution is then passed through a Millipore* bacterial filter to ensure sterility. Twenty microcuries are used in patients under twenty years of age, and 50 to 60 μ c for adult patients. The dose is administered intravenously at least twenty-four hours prior to scanning.

The pulse height analyzer is adjusted to count strontium 85's single 0.51 mev. gamma centered in an 80 kev. window. The 19 hole, coarse focus collimator is used with a small oblong (1×4 mm.) light shaper. Line-spacing is adjusted to 0.4 cm. The

count per minute range differential is set at 10 per cent of a 1K scale and the film density setting is 100. Scanning speed is 16 to 20 CM./min. The average bone lesion counts 500 CPM above surrounding bone tissue. Identifying marks are placed on the film. Lead overlays are used to properly mark the roentgen-ray film and the two are superimposed (Fig. 11).

DISCUSSION

Strontium 85 has a half-life of 65 days. It decays by electron capture to metastable rubidium 85 which emits a single gamma photon of 0.51 mev. and becomes stable Rb^{85} . Of the administered dose, approximately 55 per cent is excreted by the fifth day¹ and the remaining strontium 85 remains relatively fixed in bone. Correcting for 50 per cent excretion, one may estimate the total whole-body dose to a standard man at 0.326 rad with a bone dose of approximately 2.28 rads.

The feasibility of photoscanning bone lesions with strontium 85 has been previously reported by this laboratory.¹⁰ Significant localization of strontium 85 has been observed in pathologic and traumatic fractures, metastatic cancer, eosinophilic granulomas, chondromas, osteomyelitis and Paget's disease. The technique makes possible an easy assessment of osteoblastic activity.

SUMMARY

Technical details of photoscanning various body organs have been discussed. All organs may be scanned except the pancreas. Recently Blau and Manske⁶ have presented details of an experimental technique of pancreatic scanning utilizing Se^{75} , seleniomethionine, and it is anticipated that a technique for pancreatic photoscanning in humans will soon be devised. Closed circuit television by enhancing contrast has proven a valuable adjunct to available commercial photoscanning equipment. Medical photoscanning has progressed sufficiently technically so that it may now take its place in the diagnostic

* Millipore Filter Corporation, Bedford, Massachusetts.

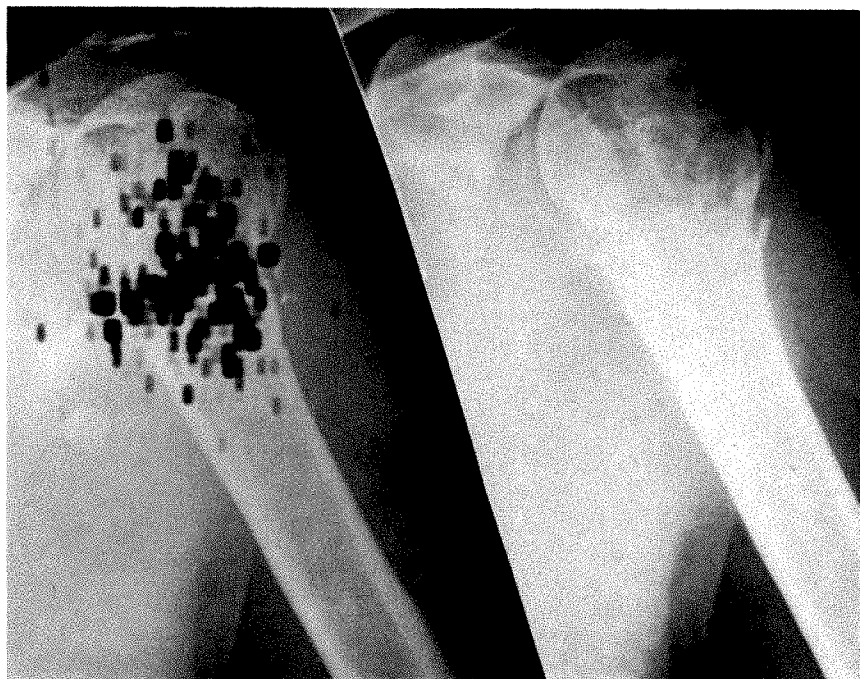


FIG. 11. Sr^{86} localization in traumatic fracture of surgical neck of humerus. Scan done 24 hours post $50 \mu\text{c}$ of Sr^{86} . (Reproduced with permission of *Radiology*.)

armamentarium of all leading hospitals. With it an atraumatic evaluation of body organs without mortality or morbidity can be accomplished.

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• DETECTION OF LIVER TUMORS WITH COLLOIDAL RADIOGOLD*

A NEW METHOD OF HIGH-CONTRAST PHOTOSCANNING

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ROTTERDAM, NETHERLANDS

IN THE first method used for detection of space occupying lesions of the thyroid gland, the distribution of radioactive iodine in the gland was studied by measuring the radioactivity from point to point and by mapping the registered number of counts per minute. The drawbacks of this method are obvious. The detector had to be directional and this was achieved by a collimating device: a gamma-absorbing shield with a cylindrical aperture. The gamma rays entered the detector through a narrow cylindrical canal and thus only a small part of the sensitive volume of the detector was used. It is clear that good resolution and directionality of the collimator were achieved at the cost of sensitivity.

The statistical reliability of radioactivity counting depends on the number of impulses counted. As collimation diminishes the efficiency of the system, it is necessary to count for a rather long time in order to obtain a fair reliability. The resolution of the collimator is usually much better than the resolution of the point countings; in practice it is impossible to choose the distance between the points so small as to equal the resolution of the collimating system, for then the whole procedure would take far too much time. Even with the unavoidable compromises—a distance of 1 to 1.5 cm. between points and a counting time of not more than two minutes per measurement—the manual scanning examination of such a small region as the thyroid gland takes an hour and a half or more.

Obviously, the above mentioned method is too time consuming, possesses a rather unsatisfactory over-all resolution and shows but a moderate statistical reliability.

These drawbacks can partly be remedied by making the scanning movements continuous and automatic and by increasing the sensitivity of the detecting device. An automatic scanning machine was built that is capable of scanning continuously. The speed of the scanning can be varied from 7.5 cm. per minute to 65 cm. per minute and the distance between sweeps may be changed in increments of 1 mm. from 2 to 17 mm.

The over-all resolution is now dependent mostly on the resolution of the collimator. Sensitivity and statistical reliability are raised by the use of a larger detector and by using more of its sensitive volume.

COLLIMATION

For the detection of space occupying lesions in the liver or in any voluminous organ, the parameters for the design of a suitable collimator are resolution, efficiency, directionality and depth response. Greater efficiency can be achieved by the use of a scintillation detector with a large crystal and a large aperture in the collimator. A good resolution calls for a small aperture in the gamma-absorbing shield. Satisfactory directional response can be obtained by providing the collimator with a single long narrow canal. The depth response of a single-hole collimator, however, is far from ideal for the radioisotope scanning of a voluminous organ because of the well-known inverse square law. The ideal collimator should have a uniform response to the radioactivity in the tumor, independent of its depth in the liver.

The combination of these postulates—highest efficiency, strong directionality, depth response not obeying the inverse

* From the Isotope Laboratory of the Rotterdams Radio-Therapeutisch Instituut, Rotterdam, Netherlands.

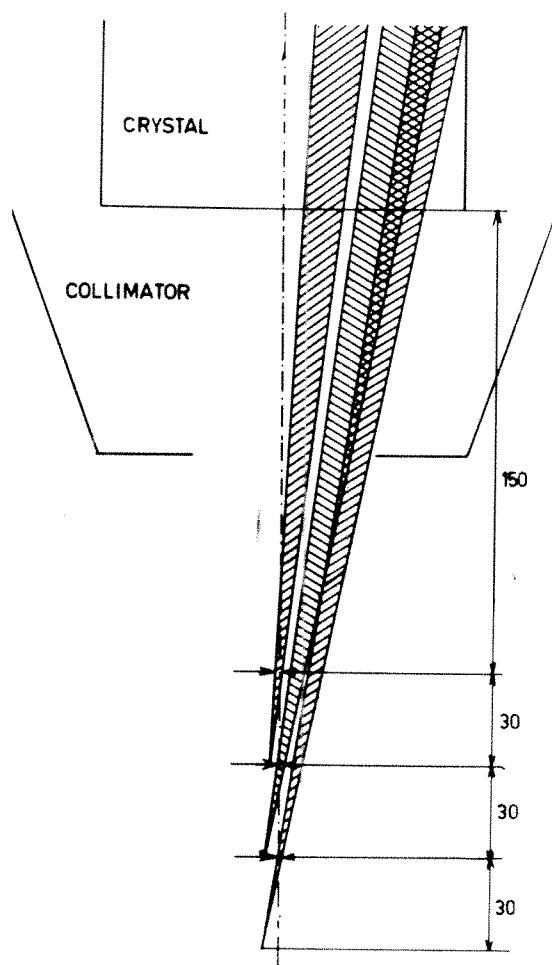


FIG. 1. Schematic drawing of the 36-channel multifocussing collimator.

square law and a resolution about equal to the diameter of the smallest tumor one hopes to detect—was met by the choice of a scintillation detector with a 6×6 cm. sodium-iodide crystal activated by thallium, a single-channel pulse height analyzer and the design of a 36-channel focusing collimator with three foci.

The thirty-six tapered channels in the gamma-absorbing shield are arranged in three groups, each with a separate focus: the first at 15, the second at 18 and the third at 21 cm. from the front of the crystal. The distance between the front of the crystal and the front of the collimator is 8 cm. (Fig. 1). In this way uniform depth response is partly met. This response, how-

ever, can be made much more ideal by counteracting the inverse square law. This may be done either by assigning more channels to a distant focus than to a more proximal one or by increasing the diameter of the channels that focus on a more distant point. This last method was used in the design of our collimator. The ratios of the surfaces of the channels with the first (15 cm.), second (18 cm.) and third (21 cm.) focus distance are 15^2 , 18^2 , 21^2 so as to counteract the influence of the inverse square law (Fig. 2).

Yet another principle was used in the collimator design. The focal distance of a single channel is made longer than the focal distance of the group of channels it belongs to. In this way the resolution of the collimating device is favorably influenced. Figures 3 and 4 show the isoresponse lines for the collimator. These response curves are constructed for radioactive spheres with a 1 cm. radius and a 1.5 cm. radius. The isoresponse lines, identical for I^{131} and Au^{198} , show that this collimator has an almost ideal characteristic. From the surface to a depth equal to the maximum diameter of the liver, the response hardly changes. If we consider the maximum response for the 1 cm. radius sphere as 100 per cent, the 80 per cent line reaches from 3 to 15 cm. depth and the 50 per cent line from 3 to 21.5 cm. depth. For the 1.5 cm. radius sphere these distances are even better:

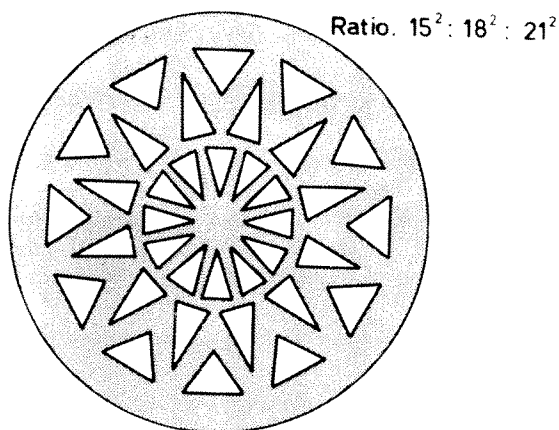


FIG. 2. Top view of the collimator.

from 3 to 18.5 cm. for the 80 per cent line and from 3 to 25 cm. for the 50 per cent line.

STORING AND PRESENTATION OF DATA

The impulses from the scintillation detector are fed through a linear amplifier and a single channel analyzer to a counter with a mechanical register. The pulse that actuates the register is used to trigger a small neon-gas discharge tube. This neon tube, mechanically coupled to the scanning detector, might with a simple optical system register all the data on a photographic film. Such a photographic recording is a convenient means of data presentation. Seldom, however, does it present the data in

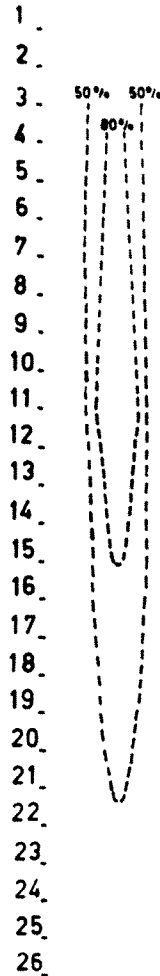


FIG. 3. Isoresponse lines (I^{131} , 360 kev.) with the 36-channel collimator for a 1 cm. radius sphere; channel width 5V.

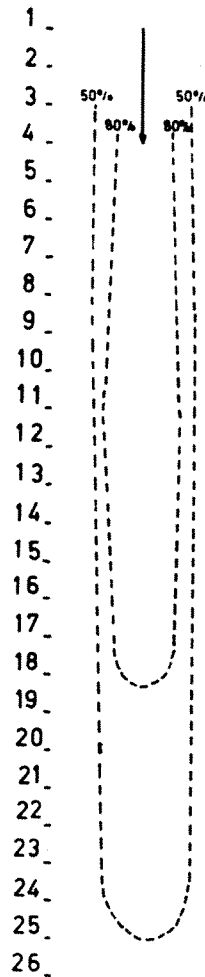


FIG. 4. Isoresponse lines (I^{131} , 360 kev.) with the 36-channel collimator for a 1.5 cm. radius sphere; channel width 5V.

a readily interpretable form. The human eye lacks the faculty of discerning the very small differences in blackening of the film caused by minor differences in count rates.

According to Bender and Blau¹ a photographic system to be successful must have a high and variable contrast and a variable gain. In their system, Bender and Blau feed the pulses from a scanning scintillation probe to a count ratemeter and have the output of the ratemeter vary a resistance in series with a scanning light bulb. In this way small differences in count rate are made visible because of the strong dependence of the light output of a tungsten

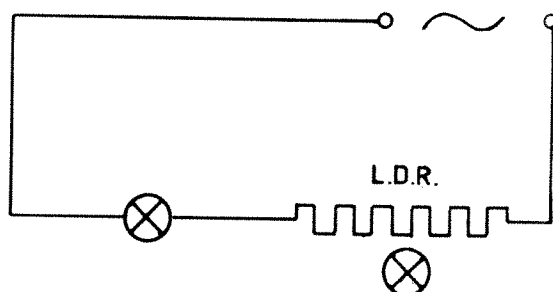


FIG. 5. Diagram of the contrast amplifier system. L.D.R.=light dependent resistor.

filament on small changes in applied voltage. This ingenious system has the drawback of the RC-time of the ratemeter. The chosen time constant, for reasons of statistical reliability, cannot be too short. This means that there will be a lag in the registration, and, unless registration during every second sweep is prevented, distortion of the registered data will occur.

The contrast amplifier system developed in our Institute is diagrammatically shown in Figure 5. The neon tube, triggered by the output pulses from the single channel analyzer, is monitored by four light dependent resistors in parallel. The frequency of the flashes from the neon tube varies linearly with the count rate and so does the illumination of the light dependent resistors (L.D.R.) (Fig. 6). The scanning bulb in our system is in series with these

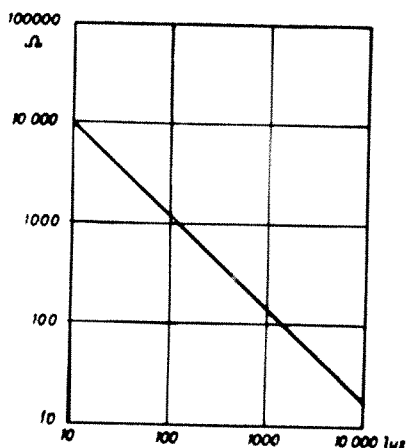


FIG. 6. Linear variation of light dependent resistor with illumination.

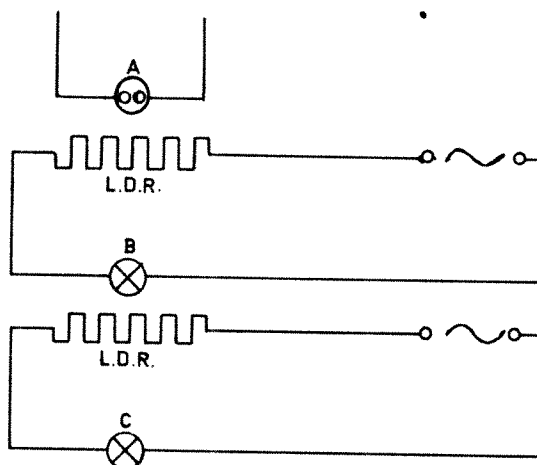


FIG. 7. Diagram of the second stage contrast amplifier system. L.D.R.=light dependent resistor; A=neon tube; B=incandescent bulb; C=scanning bulb.

L.D.R.'s and its tungsten filament flashes synchronously with the neon tube, but the brightness as well as the frequency of these scanning flashes varies with the count rate, and thus a marked nonlinear contrast response is obtained without the introduction of inertia from a ratemeter circuit. The gain of the contrast amplification is easily varied by changing the voltage in series with the L.D.R.'s and the scanning bulb. Background suppression, too, is achieved by this means.

A second stage contrast amplifier system, shown in Figure 7, can be built. Neon tube A varies the resistance of a number of L.D.R.'s in parallel and thus influences the light output of the incandescent bulb B which illuminates a second chain of L.D.R.'s that control the voltage on the scanning bulb C. Feed back should be prevented in this system.

There is always the danger of loss of information. One of the ways in which contrast information may be lost is by registering in the saturation region of the film sensitivity curve. To prevent this, moderate contrast amplification is used and the registered data are analyzed by transilluminating the film and viewing it on a closed-circuit television system. By changing contrast and brightness controls and

varying the video-gain, all degrees of film density are visualized. In this way even minor differences in count rate can be detected without the danger of not recording important data or losing data because of registration in the saturation region of the photographic film.

TECHNIQUE

Radioactive colloidal gold (Au^{198}) (N.V. Philips Duphar, Amsterdam, Netherlands) is given intravenously in a dose of $250 \mu\text{c}$. The mean particle size is 5μ . Scanning is started not earlier than thirty minutes after injection, but most often is performed four to five hours after the administration of the colloidal radioactive gold. The patient is examined in the supine position and the collimator is held at such a distance that no contact is made with any point of the body. This distance is not too critical, however, because of the special design of this collimator and the resulting isore-sponse lines. Pulse height analysis and contrast amplification are used (Fig. 8).

The whole procedure takes ten minutes for positioning and thirty to forty-five

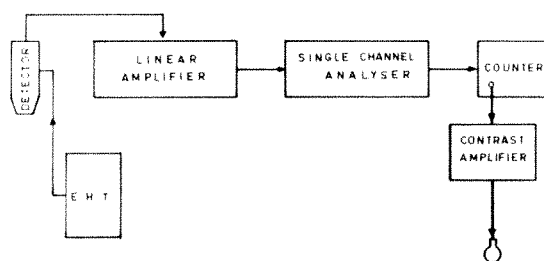


FIG. 8. Block diagram of the set-up.

minutes for the actual scanning. The examination may be repeated twenty-four and, if needed, even forty-eight hours after the administration of the nuclide.

INTERPRETATION

The developed negative is viewed in front of a view-box on a closed television circuit. By changing the light intensity of the view-box or the diameter of the optical diaphragm, varying the contrast control and brightness control and adapting the video-gain, all minor variations of film blackness can be detected (Fig. 9, *A* and *B*). It is important to look not only for differences in blackness but also in con-

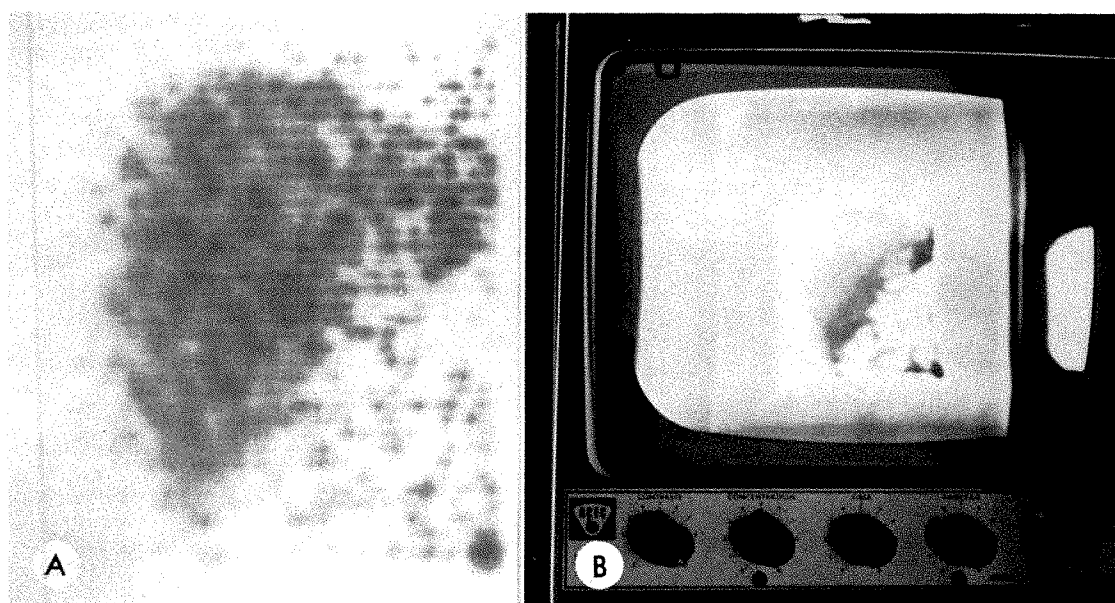


FIG. 9. (*A*) Scintiscan and (*B*) its televised image show normal configuration of the liver. Multiple round areas of clearly diminished radioactivity are seen on the television screen, representing metastatic foci from primary carcinoma of the breast.

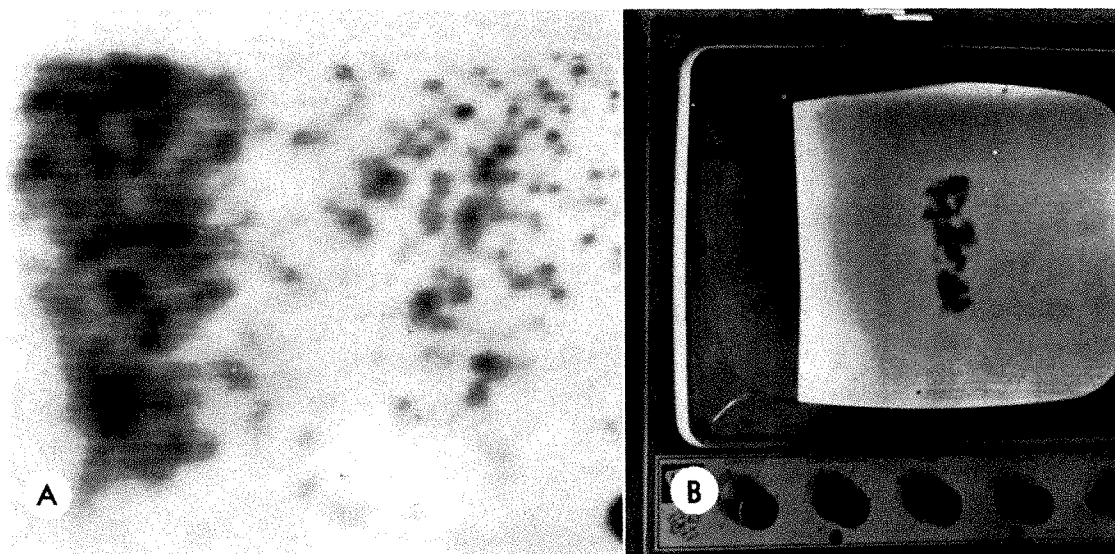


FIG. 10. (A) Scintiscan and (B) its televised image. The scintiscan shows an enlarged liver. The left lobe exhibits only a small amount of radioactivity at its left margin. The larger part of the left lobe shows no uptake at all. Irregular uptake is noted in the right lobe. On the television screen multiple round defects in the right lobe can be seen, due to metastatic melanoma malignum, verified by autopsy.

figuration. The shape of metastases on the scintigram is more or less round. One gets the impression that the defects due to cirrhosis are more irregularly shaped (Fig. 10, A and B). Moreover, the differences in thickness between the right and left lobe should be kept in mind. The radioactivity

increases in the scanning field from left to right and so does the blackening of the film (Fig. 11, A and B). At the lower margin of the liver, the hepatic hilus influences the distribution of radioactivity and often a rather large "defect" can be visualized in this region by television techniques. Since

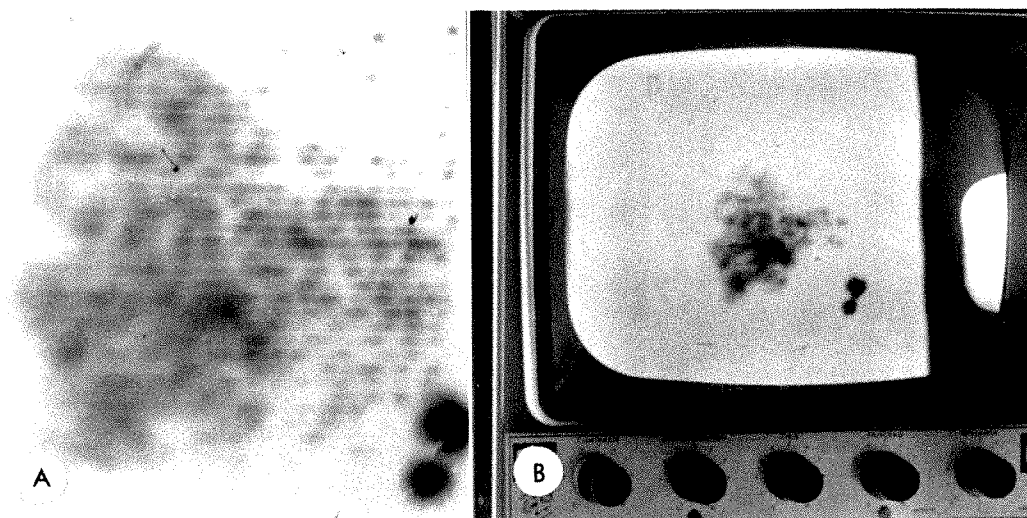


FIG. 11. (A) Scintiscan and (B) its televised image. The scintiscan shows defects at the right border of the liver and some space occupying lesions at the lower and upper border can be suspected. These lesions are much more distinct on the television screen. The diagnosis was that of metastases from carcinoma of the breast.

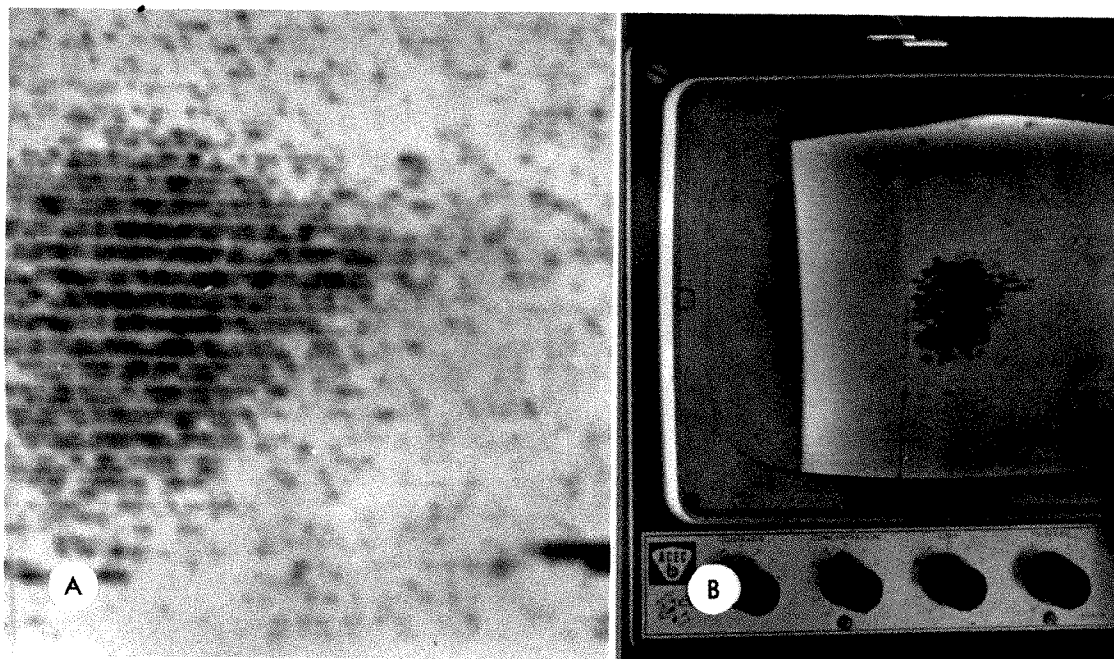


FIG. 12. (A) Scintiscan and (B) its televised image. The scintiscan shows no evidence of metastases; however, distinct defects are seen on the television screen, suggesting the presence of metastases (from a primary carcinoma of the esophagus).

respiration causes up-and-down movements of the liver, it reduces the possibility of detecting small space occupying lesions. A single tumor with a radius smaller than 1 cm. will therefore not be detected with this system. In a non-moving phantom, an area of reduced activity with a radius of 1 cm. is easily recognized with our system. Geometric factors are of little importance since the collimator is specially designed for scanning voluminous organs (Fig. 12, A and B).

SUMMARY

The shortcomings of manual scanning with point-to-point counting are analyzed and the desirable characteristics of a scanning method for the examination of voluminous organs are described.

The importance of collimation is stressed and the isoresponse lines of a multifocus 36-channel collimator which was developed

especially for scanning large organs are shown. Of importance, too, is registration with adequate contrast enhancement. A contrast amplifier without inertia has been developed. For this purpose light dependent resistors are used. For an analysis of the registered data, the processed film is viewed on a closed-circuit television system.

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THE USE OF I^{125} TO INCREASE ISOTOPE SCANNING RESOLUTION*

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THE probability of detecting a "cold" lesion in an organ such as the liver or thyroid by isotope scanning depends on both the absolute count rate and the contrast or target-nontarget ratio over the lesion. The contrast ratio over a lesion on the surface of a large organ like the liver, is considerably reduced by high-energy radiation originating in the tissues beneath the cold lesion and penetrating through it to the collimator system. It occurred to us that the contrast ratio could be increased considerably by the use of a radiation source emitting low energy gamma radiation or x-radiation, since photons originating deep in the organ would be largely attenuated before reaching the detector, while photons originating from more superficial regions would still be detectable.^{7,8,9}

Using conventional methods with I^{131} rose bengal or colloidal gold 198 for liver scans, practical considerations limit the collimator design to a field of view approximately 1 inch in diameter, and the detection of cold nodules much smaller becomes virtually impossible.^{4,6} In the thyroid, where the mass of tissue surrounding the cold nodule is much smaller and the available photon flux is higher, a collimator with a field of view 5 to 6 mm. in diameter at the focus may be used and cold nodules of this size may be demonstrated under favorable conditions.⁵ One of the principal objectives of this investigation was to evaluate the possible improvement in resolution which might be obtained by using lower energy photon emitters.

EXPERIMENTAL

Two apparently suitable sources of low energy radiation are palladium 103, whose

principal radiations, the rhodium $K\alpha$ and $K\beta$ photons, have energies of 20.2 and 23 kev., and iodine 125, whose observable photon radiations are the tellurium $K\alpha$ and $K\beta$ lines with energies of 27.4 and 31.2 kev. respectively, and the small unconverted fraction of the 35.4 kev. gamma. The narrow-beam half-value layers for these radiations are very nearly 1.0 cm. and 2.0 cm., respectively, in tissue.^{9,10}

A variety of phantoms was constructed to represent the liver and thyroid containing cold lesions of various sizes and locations. These phantoms were made of slabs of 12 per cent gelatin, 4 inches in diameter by $\frac{1}{2}$ inch thick and contained the isotope in solution with cylindrical lucite plugs to represent the cold nodules. Figure 1 shows count rate profiles across 6 such liver phantoms containing palladium 103, iodine 125 and iodine 131, and having lesions 1 inch in diameter by 1 inch thick in two locations, one on the surface of the liver and the other 1 inch below the surface. In both cases, 1 inch of overlying tissue was present, and the thickness of the liver was 4 inches. A 2×2 inch sodium iodide crystal with a 5 ml. beryllium window was used with the same collimator for all measurements. The collimator, which had a 2 inch focal length and a $\frac{1}{2}$ inch circle of view at the focus was designed so that 1 per cent of the observed counts for I^{131} represented 364 kev. photons which had penetrated the collimator septa. The focal point of the collimator traversed the center of the "lesion" during the scan. A single channel pulse height analyzer was used to observe the principal photopeak of each isotope.

Similar measurements were made on thyroid phantoms constructed of $\frac{1}{2}$ inch

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PHANTOM: 1" COLD NODULE IN LIVER, 1" OVERLYING TISSUE

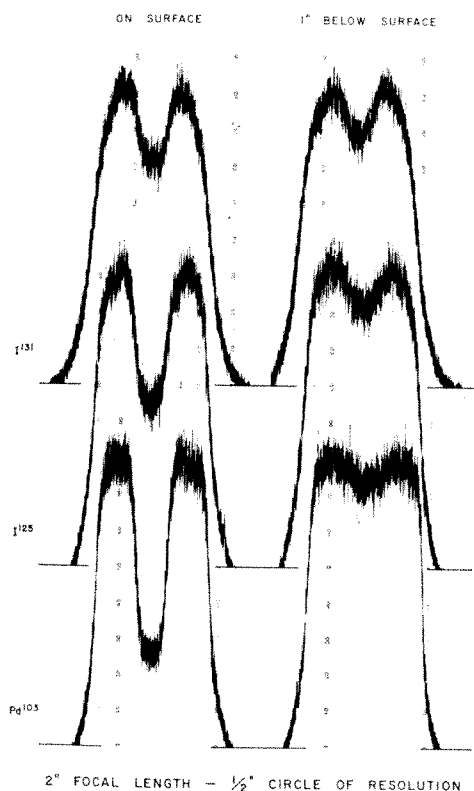


FIG. 1. Count rate profiles across liver phantoms containing I^{131} , I^{125} , and Pd^{103} .

slabs of gelatine containing either I^{125} or I^{131} . These were sandwiched between 1 inch of overlying and 4 inches of underlying untagged gelatine representing the other tissues of the neck. The 1 inch diameter

lucite plugs representing the cold lesions extended entirely through the $\frac{1}{2}$ inch active layer so that the collimator over the lesion was not looking directly at any of the radioactive material and registered only scattered photons.

The contrast ratios and relative count rates observed in these phantoms, normalized to the same isotope concentration, are shown in Table I. We had feared that the radiations from I^{125} , which are attenuated to a substantial degree by scatter rather than absorption, might produce an intense background of scattered radiation. As can be seen, especially in thyroid phantoms, while this phenomenon exists, it is somewhat less than the background from Compton scatter of the high energy photons of I^{131} .

Since the probability of detecting a lesion within a given time depends on the count rate as well as on the contrast, the attenuation in overlying tissue becomes critical at the lower energies. Under the conditions shown in Figure 1, the one inch of overlying tissue produces a reduction in count rate to 79 per cent for I^{131} , to 45 per cent for I^{125} and to 21 per cent for Pd^{103} . This attenuation nullifies to a considerable extent the useful increase in contrast.

The difficulty in producing a palladium compound with properties suitable for liver scanning has virtually eliminated the use of this material at the present time.

TABLE I
OBSERVED CONTRAST RATIOS

	Liver Phantoms			Thyroid Phantoms	
	Contrast Ratio		Relative Count Rates over Normal Tissue for Equal Isotope Density	Contrast Ratio	Relative Count Rates over Normal Tissue for Equal Isotope Density
	Lesion on Surface	Lesion 1 Inch below Surface			
I^{131}	.77	.87	100	.34	100
I^{125}	.58	.91	58	.30	85
Pd^{103}	.35	.96	4	—	—

TABLE II
COMPARATIVE RADIATION DOSAGE

Isotope	Rads per $\mu\text{cd/gm.}$			Total Organ Dose (rads)		
	Thyroid	Liver	Total Body	Thyroid 30 $\mu\text{c}/30 \text{ gm.}$	Liver 200 $\mu\text{c}/1.5 \text{ kg.}$	Total Body 5 $\mu\text{c}/70 \text{ kg.}$
I^{131}	120	152	200	103	.210	.010
I^{125}	130	192	272	58	.035	.014
			Agent	Iodide	Rose Bengal	Iodinated Albumin
			Biologic Half Life	50 days	2 hours	17 days

Palladium phthalocyanine sulfonate was found to have a biologic half time of about 12 days in the liver. In comparison, the half life of iodine-tagged rose bengal is a few hours.

The respective radiation dosages^{9,10} of I^{125} and I^{131} are compared in Table II. The energy from I^{125} available for producing ionization is the sum of the 35.4 kev. gamma transition and the energy of the tellurium excited state following K or L capture. This amounts to an average of 62.3 kev. per disintegration with 41.3 kev. as K and γ photons. The remaining 21.0 kev. appears as soft fluorescent photons, conversion electrons and Auger electrons, which are absorbed close to their point of origin and may be considered in dose calculations as β radiation.

Using specially designed detectors, the radiation of I^{125} may be detected several times more efficiently than those of I^{131} . Collimators may be designed¹ which are approximately 3 times as efficient for I^{125} as for I^{131} for the same configuration and field of view. Virtually all the photons from I^{125} penetrate the beryllium window, interact with the sodium iodide detector crystal and appear in the photopeak, while approximately 50 per cent of the photons from I^{131} have Compton interactions in the crystal and do not appear in the photopeak.¹⁴ In addition, I^{125} produces 1.8 times as many detectable photons per disintegration as does I^{131} .

In an attempt to bring all these different factors together for comparison under optimal conditions, the relative statistical detection efficiency was computed* for the cold nodules in the liver and thyroid phantoms described above, based on equal radiation dosage and scan time. The observed count rates were weighted according to the above mentioned factors, and the results are shown in Table III. The values in Table III may be interpreted in several ways. For instance, in the liver phantom with the cold nodule on the surface shown in column 1, the lesion could be detected 21 times faster using the I^{125} for the same radiation dosage as with I^{131} or it could be detected in the same time for 1/21 of the radiation dosage or, using the same scan time and radiation dosage as with I^{131} , a collimator with a sharper focus and result-

* Consider the count rate C_L over a cold lesion and C_t over the surrounding tissue. In time T , $C_L T$ and $C_t T$ counts will be accumulated over these regions. A statistical measure of the difference between these two counts is the number Z of standard deviations of the difference contained in the difference. Since Poisson formulation may be applied, the standard deviation of the difference is $\sqrt{C_L T + C_t T}$ and

$$Z = \frac{C_L T - C_t T}{\sqrt{C_L T + C_t T}} \quad \text{Rearranging: } T = \frac{Z^2 \left(\frac{C_L}{C_t} + 1 \right)}{C_t \left(\frac{C_L}{C_t} - 1 \right)^2}$$

T is thus the time required for a count over each region long enough to establish the existence of a difference with $Z\sigma$ confidence. T depends both on the contrast ratio C_L/C_t and the absolute count rate C_t . The reciprocal of T is taken as a measure of the statistical detection efficiency.

TABLE III
RELATIVE STATISTICAL DETECTION EFFICIENCY
For cold nodules in phantoms for same scan
time and radiation dosage

	Liver		Thyroid
	Lesion on Surface	Lesion 1 inch below Surface	
I^{131}	1.00	.30	1
I^{125}	21	.80	5.5

ant lower efficiency could be used to increase the resolution of the resulting picture.

In considering this increase in resolution, it is difficult to arrive at a precise descriptive criterion. Each situation appears to have its own special requirements. Since in both thyroid and liver scanning the lesions of interest are voids, the criterion chosen was the smallest void which could be detected with 2σ confidence from the count rates over the void and the surrounding tissue. In the case of the thyroid the void was assumed to extend entirely through the gland as in the experiments described. In the case of the liver, the void was assumed to have a depth equal to its diameter, and the field of view of the collimator was assumed to equal the diameter of the void. The diameter of the circle of view of the collimator at its focus thus becomes the measure of resolution, and the counting statistics determine the smallest usable collimator.

Using the same parameters as in Table III, it can be shown that with I^{125} a cold nodule of approximately one half the diameter should be detectable in either the thyroid or liver without exceeding the radiation dosage and scanning time used with I^{131} . The effect of reducing the diameter of the "circle of view at the focus" to one-half reduces the counting efficiency of the collimator by a factor of 4 or more depending on the configuration of the region of view. Since the time permitted for viewing a region of this size during a

scan is likewise reduced by a factor of 4 when the scan time is kept constant, the opportunity for the detector system to accumulate a statistically valid count over such a lesion is reduced by a factor of 16 or more, thus requiring at least a fourth power increase in the emitted detectable photon flux at the surface of the body or an appropriate increase in contrast or both, if statistical validity is to be maintained. These conditions are apparently achieved by substituting I^{125} for I^{131} .

The absolute dimensions of the smallest detectable lesions were estimated using the above criteria together with the efficiencies of optimal collimators.¹ Assuming, for the thyroid, 1 inch of overlying tissue, a 15 minute scan time, 100 cm.² for the area scanned, and 100 rads for dose to the gland, a lesion 6.1 mm. in diameter should be detectable with I^{131} , and 3.6 mm. in diameter with I^{125} .

For the liver, with 1 inch overlying tissue, using a scan time of 30 minutes, 600 cm.² for area scanned, and 200 mrad for radiation dosage to the liver, lesions 17 mm. in diameter on the surface and 21 mm. in diameter 1 inch below the surface should be detectable with I^{131} . The corresponding figures for I^{125} are 9 mm. and 21 mm. These numbers are, of course, based on the assumption that the liver is not moving with respiration, and must be interpreted with this reservation.

The size of a detectable lesion by this statistical criterion thus appears to be consistent with the experience gained by other investigators using I^{131} for liver and thyroid scanning and we are hopeful that the predicted figures for I^{125} may be realistic.

CLINICAL MATERIAL

The principal deterrent to the clinical and experimental use of iodine 125 has been its lack of availability. The commercially available I^{125} produced by the cyclotron bombardment of tellurium is expensive and heavily contaminated with the undesirable 13 day I^{126} . The alternative

method of producing iodine 125 by the neutron activation of xenon 124 has been developed in our laboratory to the point where curie quantities with less than 2 per cent contamination have been produced, and it now appears feasible to consider the clinical use of this material on a substantial scale.^{9,10}

As special detection equipment is not yet available for routine scanning of iodine 125, conventional unmodified equipment was used, and iodine 125 was substituted for iodine 131, microcurie for microcurie. Under these circumstances the radiation dosage to the patient except under the most unfavorable circumstances was still less than that of I^{131} (see Table II).

In the present study, comparative thyroid scans with iodine 125, and iodine 131 were made on 10 patients, and comparative liver scans, using iodine-tagged rose bengal likewise were made on 10 patients. All patients were selected on the basis of clinically suspected pathology. In all cases, iodine 125 was used first, followed by iodine 131, in order to prevent the low energy Compton scatter from the iodine 131 interfering with the low energy photons from iodine 125. Pulse height analysis was used

for both isotopes so that only the 364 kev. photopeak was observed for iodine 131 and the 27 to 35 kev. photopeak for iodine 125. The equipment was the Picker Magna scanner as described by Herring,¹¹ the 19 hole collimator being used for the liver scans and the 31 hole collimator for the thyroid scans. The thyroid patients were scanned 24 hours after administration of 50 μ c of isotope. Those patients in whom the liver was scanned were given iodine 125 and iodine 131-labeled rose bengal in doses of 3 μ c per kg., without previous administration of untagged rose bengal.

As was expected, the count rates with iodine 125 averaged somewhat lower for the liver scans—1,200 to 1,500 counts per minute with iodine 125 and 3,000 to 4,000 counts per minute with iodine 131. This is not surprising since special detectors were not used for the iodine 125 and the attenuation of radiation in the aluminum can of the crystal alone accounts for an additional loss of 40 per cent in count rate. Nevertheless, even under these circumstances, representative liver scans (Fig. 2, *A* and *B* and 3, *A* and *B*) show a remarkably improved visualization of surgically demonstrated hepatic metastases.

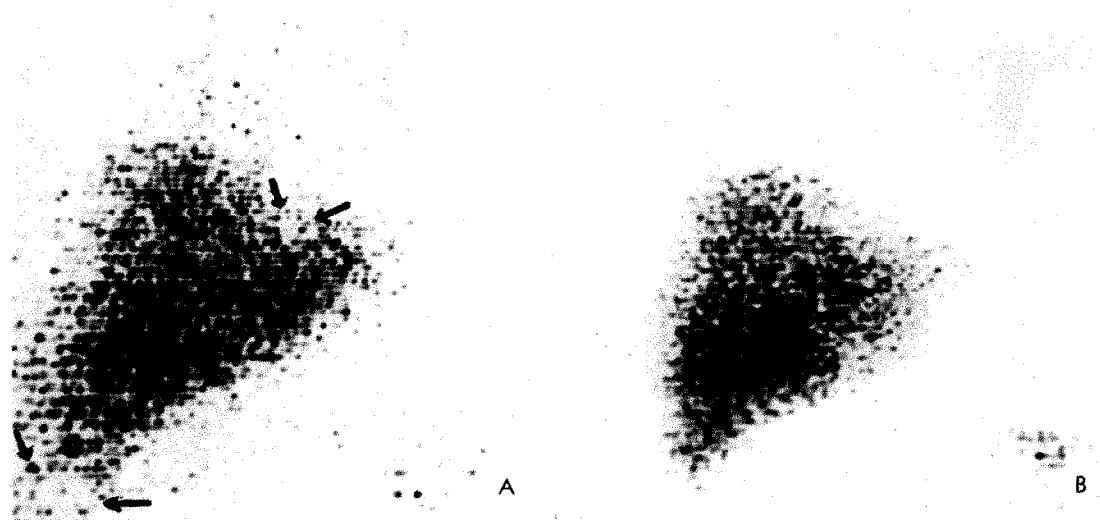


FIG. 2. Rose bengal liver scans of the same patient using (*A*) I^{125} and (*B*) I^{131} with demonstration of surgically proved metastases by I^{125} which are practically invisible using I^{131} (Picker Magna scanner, 19 hole collimator).

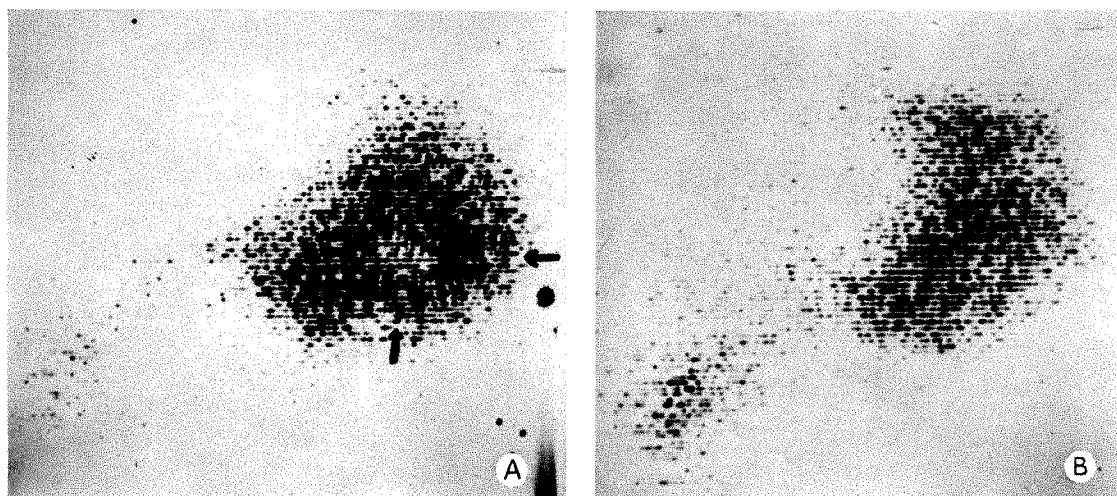


FIG. 3. Demonstration of lesion using (A) I^{125} rose bengal liver scan which is practically invisible with (B) I^{131} .

In general, the thyroid scans closely resembled those obtained with I^{131} . Cold nodules are better delineated, however, even though the count rates are lower, as observed in Figure 4, A and B which illustrates the thyroid scans of a patient with multinodular nontoxic goiter. The many nodules are clearly demonstrated with iodine 125, but almost not at all with iodine 131. The gross pathologic specimen is seen in Figure 5.

DISCUSSION

The single most consistent observation made in comparing scans made with the two isotopes is the over-all increase in contrast in scans with I^{125} . It should be pointed out that the increased contrast in cold nodules demonstrated in the liver and thyroid is not entirely equivalent to the criteria for resolution presented in the earlier part of this paper. In the clinical cases the count rates far exceed the minimal values required for "statistical detection of a lesion." The isotope contrast becomes prominent under these circumstances and produces a greatly improved picture.

It is interesting to speculate, and work is in progress at the moment to determine, how much further the picture can be improved by sharpening the collimator focus

and sacrificing count rate. It is also possible that by judicious application of background cut-off techniques the collimator focus may be sharpened in effect without as much loss in count rate. At the present time it seems completely justifiable to use I^{125} with the equipment available since, even under these unfavorable circumstances, iodine 125 appears to be as good as or better than I^{131} in terms of producing a more clearly resolved scan of the thyroid and the liver.

The methods of contrast now in use, background cut-off, and video or photographic manipulation,^{2,3} should be complementary to the "built in" contrast in I^{125} scans. It is characteristic of all these methods that some information must be sacrificed at least temporarily in order that other information may be accessible. I^{125} is no exception to the rule, as is seen in Table III. While the possibility of detecting a lesion much beneath the surface of the liver is reduced to a relatively much greater extent than with the penetrating radiation of I^{131} , it is a matter of practical experience that such lesions, unless quite large, are much more difficult to detect by any type of scanning technique. It is obvious that to be most effective the liver scan should be circumferential rather than planar, as sug-

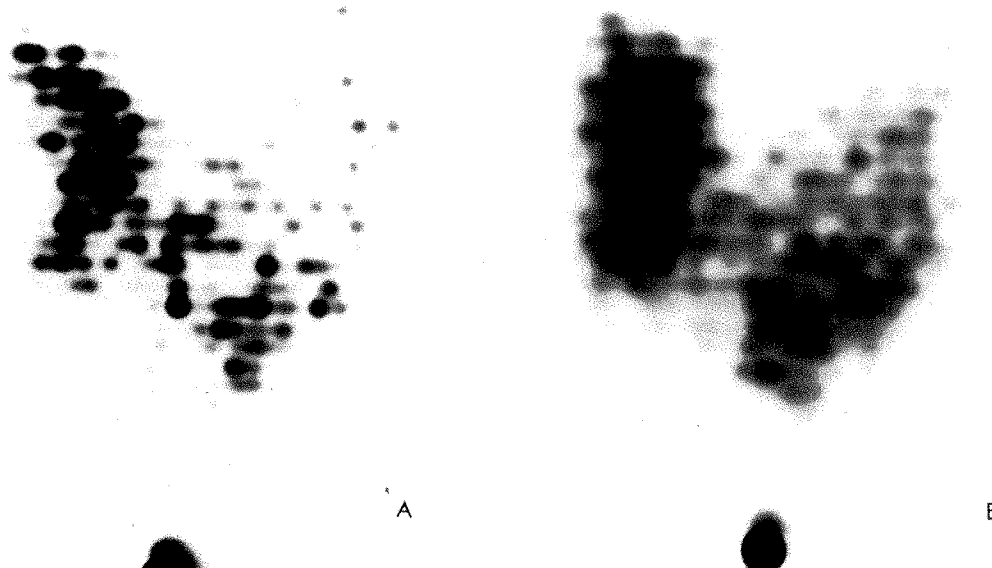


FIG. 4. (A) I^{125} and (B) I^{131} scans of multinodular thyroid, 15 μ c in gland (Picker Magna scanner using 31 hole collimator).

gested by Kuhl,¹² and under these circumstances a collimator with shorter focus and higher efficiency would be more effective, giving clearer pictures of the entire "visible" surface of the liver, and permitting visualization of lesions on the lateral and posterior aspects of the liver, at present hidden in a frontal, planar scan. The use of more efficient, shorter focus collimators introduces divergence into the region of view to a greater extent although the divergence beyond the focal point is of little importance because photons originating at this depth are largely attenuated in the overlying tissue. This circumstance and the much larger area to be looked at in a circumferential scan suggest that multiple detectors would probably achieve the best results.

While the relatively low radiation dosage to the liver produced by tagged rose bengal permits justification of efforts to increase the resolution of the liver scan, this posi-

tion is not so readily tenable in thyroid scanning, and it would appear wise to expend a considerable portion of the advantage gained from the use of I^{125} in reducing

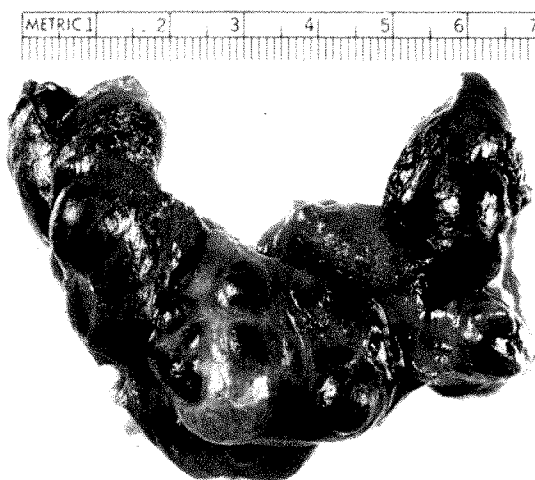


FIG. 5. Surgical specimen of thyroid shown in Figure 4, A and B.

the radiation dosage to the gland resulting from this procedure.

Other advantages accruing from the use of I¹²⁵ are the long shelf life (60 day half life), low shielding requirements, and low background possible when a thin crystal is used.^{7, 8, 9, 10, 15}

SUMMARY

Experimental and clinical studies have demonstrated that I¹²⁵ may be substituted for I¹³¹ for liver and thyroid scanning with considerable advantage. The radiation dose to the patient may be reduced, the resolution and contrast of the scan increased, and the advantage of the long shelf life of the isotope may be enjoyed even without special detection equipment. When such equipment is used, the sensitivity of detection may be increased by an order of magnitude over that of available commercial scanning devices using I¹³¹. It seems probable that the isotope will become available commercially in the near future since the technical difficulties of producing substantial quantities of adequate purity appear to have been overcome.

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SOME MODIFICATIONS OF PHOTO-SCANNING TECHNIQUES*

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THE ultimate criterion of a successful isotopic scan is its statistical validity. However, the production of a scan which yields the maximum amount of clinical information is of no less importance.

With simple modifications in the use of a commercially available photorecording scanner, excellent photoscans may be produced. This model scanner has provision for simultaneous dot scan and photorecording. The details of the engineering and electronics of this scanner may be found in an article by Herring.¹

The initial change made in the scanner was the substitution of a 31 hole fine point focus collimator for a 19 hole point focus collimator. The new collimator, as expected, greatly improved the resolution of the thyroid scans, though the efficiency of the 31 hole collimator is approximately 16 per cent that of the 19 hole collimator. The loss in efficiency has been compensated for statistically by the use of slightly larger doses of radioactive material. In the case of thyroid scanning, this has meant the use of 50 μ c instead of 10 μ c of I^{131} . Further statistical accuracy is accomplished by the reduction in scan speed from 30 to 10 cm./min. For the average thyroid scan, excluding substernal scanning, this means a total scan time of about 20 to 30 minutes, which is usually well within the range of patient cooperation, even for a person with hyperthyroidism. Of course, with liver scanning or for scans of larger surface area, time becomes a crucial factor and it is usually necessary to resort to the 19 hole collimator, a faster scan speed, and larger doses of radioactive materials. Additional improvement in counting statistics is accomplished by the use of a large scintilla-

tion crystal when using the 31 hole collimator. A 3 inch by 2 inch sodium iodide crystal is used in this particular instrument.

Preliminary scans were made with a lucite phantom, shaped to simulate the actual size and contour of the human thyroid. The phantom contains three lucite dowels measuring 13 mm., 10 mm. and 6 mm., respectively (Fig. 1). The phantom was also constructed so that the left lobe is half the depth of the right lobe. Hence, at any moment the left lobe contains half the radioactivity of the right lobe. An 11 mm. hole is placed in the left lower lobe (Fig. 1)

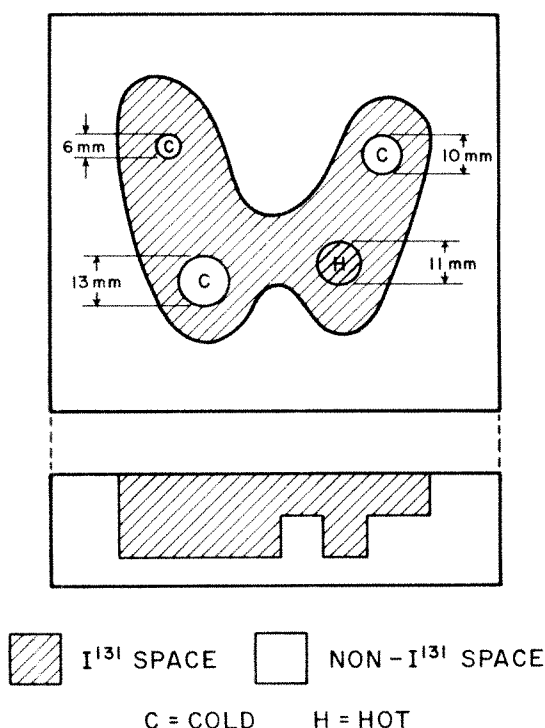


FIG. 1. Lucite phantom with three "cold" nodules and one "hot" nodule.

* From the Department of Radiology, the University of Chicago, Chicago, Illinois. Delivered at the meeting of The Society of Nuclear Medicine, June 23-25, 1960.

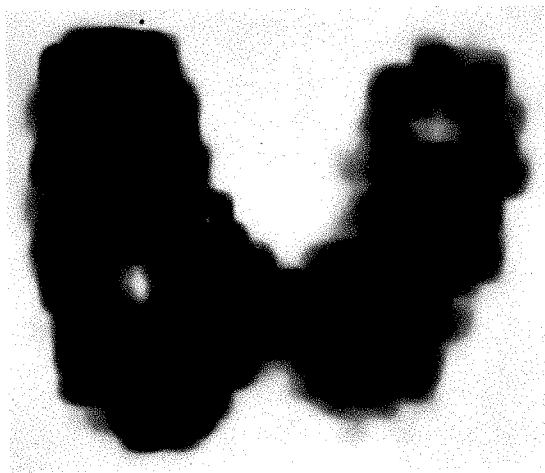


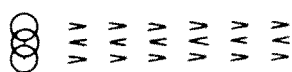
FIG. 2. Original photostatic scan of the phantom. The over-all density is too great and resolution is lacking.

to simulate a "hot nodule;" the three dowels are designed to represent "cold nodules." The phantom is filled with approximately 10 to 15 μC of I^{131} which is the amount one might expect to be concentrated by a euthyroid gland, assuming an

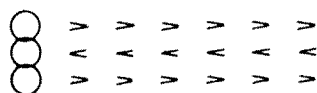
average uptake in the range of 20 to 30 per cent and using an administered dose of 50 μC .

Despite the modifications mentioned, the original scans of the phantom lacked significant detail (Fig. 2). Only the largest of the three cold nodules was resolved. The over-all density of the scan was obviously too great. The photorecording dot overlapped and covered every point on the film twice, thus causing double exposure. In an attempt to eliminate this overexposure due to overlap, the index spacing was increased (Fig. 3). Unfortunately, because there is no provision for separate spacing of the dot scan and photostatic scan, increasing the spacing between the photorecording dot automatically caused the width between the lines of the dot scan to be too wide for accuracy. The next step was obvious. A 1.5 mm. light collimator was placed over the cathode tube light source, which, when uncollimated, measured 5 mm. in diameter (Fig. 4). Without any other change, the use of the small bore light collimator gave scans

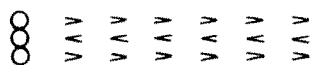
PHOTOSTATIC



EXCESSIVE OVERLAP



CORRECT SPACING

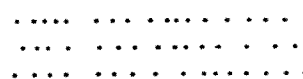


CORRECT SPACING

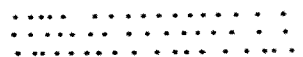
DOT SCAN



CORRECT SPACING



EXCESSIVE SPACING



CORRECT SPACING

FIG. 3. Diagrams showing the effect of proper and improper index spacing using the large photorecording dot. The last line shows how this problem is corrected by the use of the small bore light collimator.

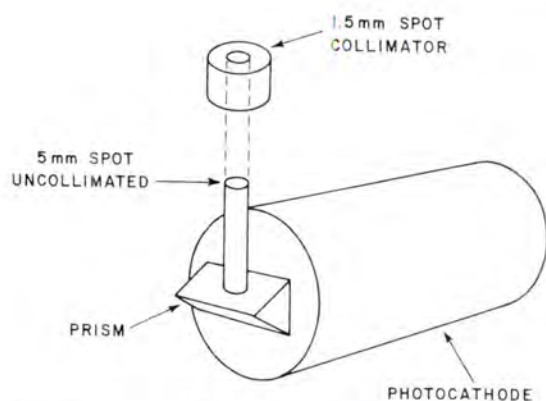


FIG. 4. Diagram illustrating the method used to collimate the photocathode light source.

with superior resolution. Figure 5 shows a scan of the same phantom as illustrated in Figure 2 but now all three cold nodules and the single hot nodule are well defined. Moreover, the difference in the amount of I^{131} on the two sides of the gland is readily apparent.

Up to this point, the control settings for photoscanning were used exactly as recommended by the manufacturer. However, with the modifications described, certain of these control settings were changed to further improve the results. The scanner has a pulse height analyzer. Since all of our scans have utilized I^{131} or compounds containing I^{131} , we have set the pulse height analyzer with a base line of 300 volts and a 10 volt window above this level. The utilization of differential counting lowers the count rate efficiency but enables one to count only the photoelectric peak of I^{131} (364 kvp.) and reject the Compton scatter of lower energy value.

Except for spacing, the control settings for the dot scan and the photoscan are separate, allowing some alteration in the dot scan without affecting the photoscan. The dot factor control determines the ratio of scintillations received by the crystal per dot recorded on the teledeltos paper. The manufacturer recommends that the dot factor be calculated on the basis of average maximum counts per minute and scan speed as follows:

$$\text{Dot Factor} = \frac{\text{Average Maximum Counts per Minute}}{\text{Scan Speed} \times 6}$$

We have found that the use of 12 instead of 6 as a constant in the denominator gives dot scans of better resolution.

Setting the count rate, range of counts, and time constant is done in the same way as with any counting device. However, there are two notable exceptions with this scanner. One is the density control; the other is the counts per minute range differential control (C.P.M.R.D.).

These two controls directly affect the density and contrast of the photoscan and have no effect on the dot scan. The recommended density setting is based on scan speed and average maximum counts per minute as follows:

$$\frac{\text{Average Maximum Counts per Minute} \times \text{Density}}{\text{Scan Speed}} = 4,000$$

Using the small bore light collimator as described, it is frequently desirable to employ a density setting of twice the calculated setting. This will theoretically make every dot on the scan twice as black. However, experience has indicated that scan density is rarely as important diagnostically as scan contrast, since contrast is the one factor which will enable the eye to differentiate an area which has increased or decreased activity compared to the rest of the organ being scanned. This, of course, is crucial for the discrimination of hot or cold nodules from surrounding tissue.

Contrast is determined by a host of factors which include scan speed, type of collimator, amount of radioactive material used, inherent film contrast, developing technique, and the counts per minute range differential setting. Most of these factors can be kept reasonably constant. We used the same scan speed, a 31 hole collimator, and a similar amount of radioactive material for all thyroid scans. Routine use of

Kodak Blue Brand film and X-Omat development insures control over these factors.

The major variable surrounds the use of the counts per minute range differential setting. In theory, this circuit is designed so that the count rate range of the tissues being scanned can be superimposed upon the density limits of the film being used. For example, in surveying a neck for thyroid scan, it might be found that the counting rate varied from 10,000 counts per minute over the gland to 2,000 counts per minute over the neck. The counts per minute range differential can now be set so that at 2,000 counts per minute the dot density recorded on the film will equal 0.3, which should be just above the base fog level of the film. The upper limit of 10,000 counts per minute can then be made to give a film density of 2.0, which should be opaque black (Fig. 6). This should yield a photoscanner of long scale or low contrast.

In most instances this type of photoscanner should give a maximum amount of information. However, should a scan of high contrast be desired, perhaps to separate tissues having count rates very close to each other, this can be done. The contrast can be increased by setting the counts per minute range differential control to a lower value than calculated. The count rate

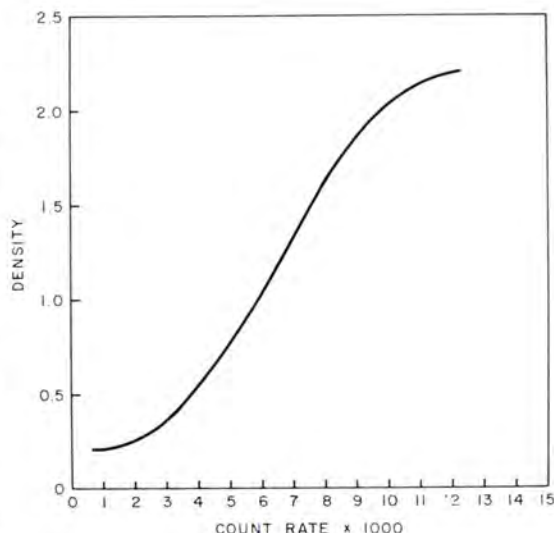


FIG. 6. Graph illustrating how the target to non-target count rate ratio is superimposed upon the film density latitude.



FIG. 5. Photoscanner of the same phantom as in Figure 2 using a small bore light collimator.

circuit, which normally causes the cathode to get brighter with increased count rate, will now cause an even greater intensity of cathode brightness for any given counting rate. If, for example, a thyroid nodule had a count rate of 9,000 and the surrounding gland a count rate of 10,000, a high contrast photoscanner would help to accentuate this difference, which otherwise might not have been appreciated with a low contrast scan (Fig. 7). It should be noted, however, that an adjustment which yields a short scale or high contrast photoscanner will necessarily mean the loss of important detail (Fig. 8), which usually is undesirable.

Frequently, when a patient who is suspected of having a nodular thyroid or carcinoma of the thyroid is referred to the isotope laboratory for a scan, one does not know beforehand whether the nodules being scanned are "hot" or "cold." Therefore, it is best not to employ the high contrast technique of scanning unless preliminary scans suggest evidence that the nodules are in a density range which might be difficult to interpret, due to the statistical variations in the scan itself. Such instances warrant a rescanning of these areas employing a lower counts per minute range

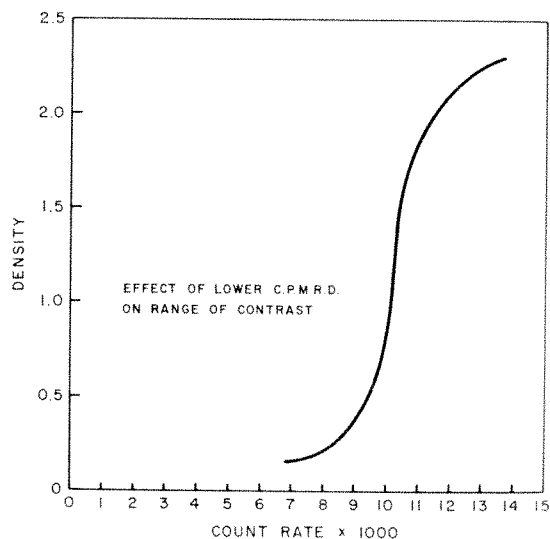


FIG. 7. Graph illustrating how a high contrast effect can be obtained by using a lower counts per minute range differential (C.P.M.R.D.) setting in order to accentuate the target to nontarget ratio.

differential setting for greater contrast enhancement.

SUMMARY

Experience with a commercially available thyroid scanner has led to the adoption of the following modifications in technique which have resulted in greatly improved photoscans:

1. Use of a 31 hole fine point focus collimator.
2. Use of slow scan speeds—10 cm. per minute for the average thyroid scan.
3. Use of a small bore light collimator on the cathode light source.

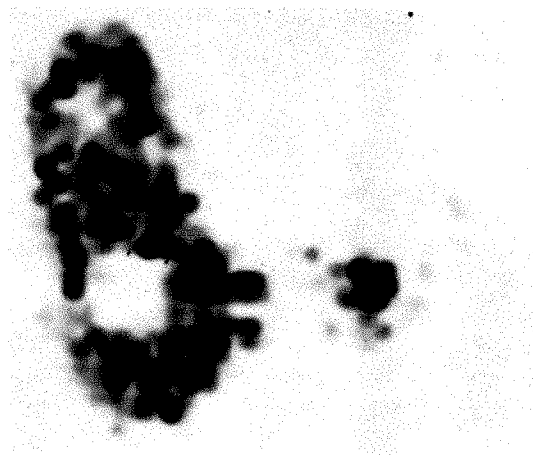


FIG. 8. Photoscan illustrating the effect of using a lowered counts per minute range differential setting to exaggerate the target to nontarget ratio. Note that significant detail is lost from the upper portion of the left lobe by this method.

4. Use of proper development time and solutions.

5. Use of proper density and contrast settings. In general, the low contrast, long range scale is found to yield the most information.

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DELINEATION OF HUMAN KIDNEYS BY SCINTILLATION SCANNING*

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DELINEATION of renal parenchyma by scintillation scanning techniques will extend and support diagnostic information obtained from intravenous pyelography, retrograde pyelography or aortic angiography. The purpose of this paper is to present a simple method of renal scanning using I^{131} labeled iodopyracet (diodrast) or ortho-iodohippuric acid (hippuran) with pertinent radiation data. Our experience in scanning 60 patients with a variety of renal disease including tumor, pyelonephritis, vascular hypertension, congenital abnormalities, hydronephrosis and renal injury will be presented together with illustrative roentgenograms and scans. While renal scanning using Hg^{203} - Hg^{205} labeled chlormerodrin has been reported to be successful,^{2,4} there are advantages in the use of a rapidly excreted I^{131} labeled contrast medium. These advantages will be presented with illustrative data.

METHOD AND MATERIAL

In the first 12 patients studied, 480 to 1,000 μ c sterile diodrast I^{131} was injected over a 2 minute period by way of a tube through which an infusion of 5 per cent dextrose in water was running. After a 1 minute flush of the tubing, the infusion was slowed to 20 to 30 drops per minute, when a second injection was anticipated. Generally, only one injection was required when kidneys were delineated at a similar level as seen on excretory urograms or supine roentgenograms of the kidneys, ureters and bladder. When one kidney was at a significantly different level, a second injection was made after completion of the scanning of one side. Although scanning was satisfactory in most patients with dio-

drast I^{131} , patients with borderline renal function failed to concentrate sufficient I^{131} in the renal area and localized it in the hepatic area. This tended to obscure the right kidney and, in normal individuals, also resulted in delayed excretion of the diodrast.

In the remaining 48 patients, 390 to 810 μ c hippuran I^{131} was used as described above with no hepatic localization seen on the scan. The dosage was estimated on the basis of body weight at 8-14 μ c per kg.

Scanning was performed with a collimator¹ having a single aperture 7/8 inch in diameter by 6 inches long, with a 1 inch by 1 inch sodium iodide (thallium activated) scintillation crystal. Prior to injection, pulse height and bias settings for counting of the 0.364 mev. I^{131} gamma rays were accomplished and scan spacing was determined from appropriate anatomic landmarks. Routine scanning speed was 0.9 cm. per second. Wherever possible, the first scanning row was located about 1.0 to 2.0 cm. above the expected location of the superior pole of the higher kidney. Usually a cephalad to caudad direction of scanning was employed. Time required for a complete study varied from 20 to 30 minutes when two injections were needed.

Serial blood samples were obtained for radioassay in 10 patients receiving diodrast I^{131} and in 12 patients receiving hippuran I^{131} ; calculations of millirad exposure to blood and whole body were done, as previously described.³ Urinary excretion was calculated from samples collected during the first 3 to 24 hours after injection of either I^{131} labeled material. Serial determinations of hematocrit, white blood cells and platelets were performed in 11 patients

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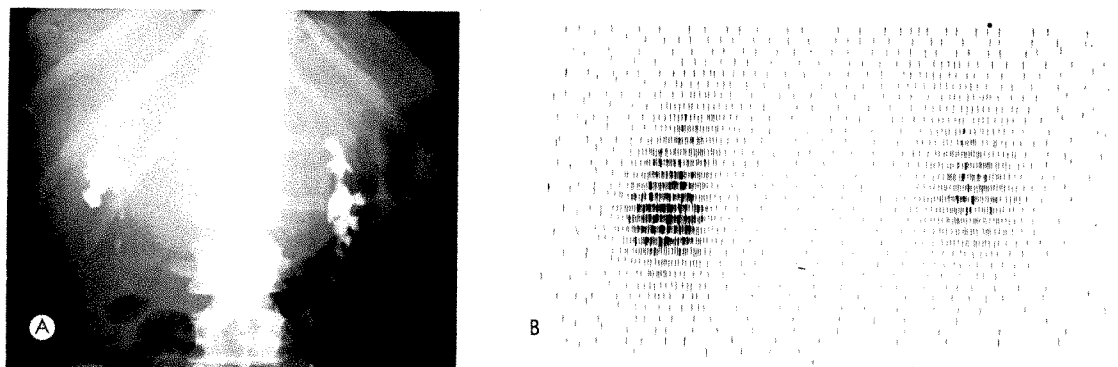


FIG. 1. Case 1. (A) Urogram. (B) Renal scan shows lateral displacement of the right kidney and a defect in the localization of I^{131} in the right upper pole. (The scan is done with the patient prone, therefore the left and right sides are reversed, as compared to the urogram which is done with the patient supine.)

receiving diodrast I^{131} . Thyroid blocking with a saturated solution of potassium iodide was carried out in patients unprotected by prior urography or studied more than 2 weeks after examinations using excretory urographic media or other iodine containing contrast media.

RESULTS

On the basis of previous work,³ it was anticipated that doses of diodrast I^{131} in the range of 2 to 2.5 mc would be required for satisfactory scanning in humans. However, doses of 480 to 1,000 μ c proved adequate and resulted in whole body radiation exposures ranging from 38 mrad in the first 48 hours to 123 mrad in the first 24 hours. A significant rise in blood radioactivity occurred between 20 and 45 minutes after injection, supporting the evidence obtained in scanning for significant hepatic localization. When hippuran I^{131} was used, the radiation exposure ranged from 31 to 125 mrad during the first 24 hours after injection. A rough inverse correlation of renal function and exposure was seen in both groups studied. Satisfactory renal scanning was performed in several patients in whom excretory urography could not be done because of blood urea nitrogen retention of 40 to 70 mg. per cent. Serial determinations of hematocrit, white blood cells and platelets revealed no

changes which could be attributed to radiation exposure.

Seventy-seven scans were performed in 60 patients with clinical diagnoses as follows: normal renal function and pyelographic studies, renal carcinoma, renal cyst, polycystic disease of the kidneys, horseshoe kidneys, pyelonephritis, hypertension due to renovascular disease, hydronephrosis, and renal injury. Case reports with illustrative renal scans and urographic studies have been chosen for each disease category listed.

ILLUSTRATIVE CASES

CASE I. A fifty-four year old man presenting with metastatic papillary carcinoma to the cervical lymph nodes was investigated over a 6 month period to determine the primary origin of the tumor. The urogram is shown in Figure 1A. At exploratory laparotomy, a tumor was found in the superior pole of the right kidney; massive extension into the retroperitoneal tissues had occurred. Figure 1B is the scan obtained in this patient.

Comment. The scan (Fig. 1B) shows lateral displacement of the right kidney and a defect in I^{131} localization in the right upper pole.

CASE II. A seventy-seven year old man presented with abdominal pain, weight loss and weakness. Retrograde urography (Fig. 2A) suggested tumor deformity of the left upper

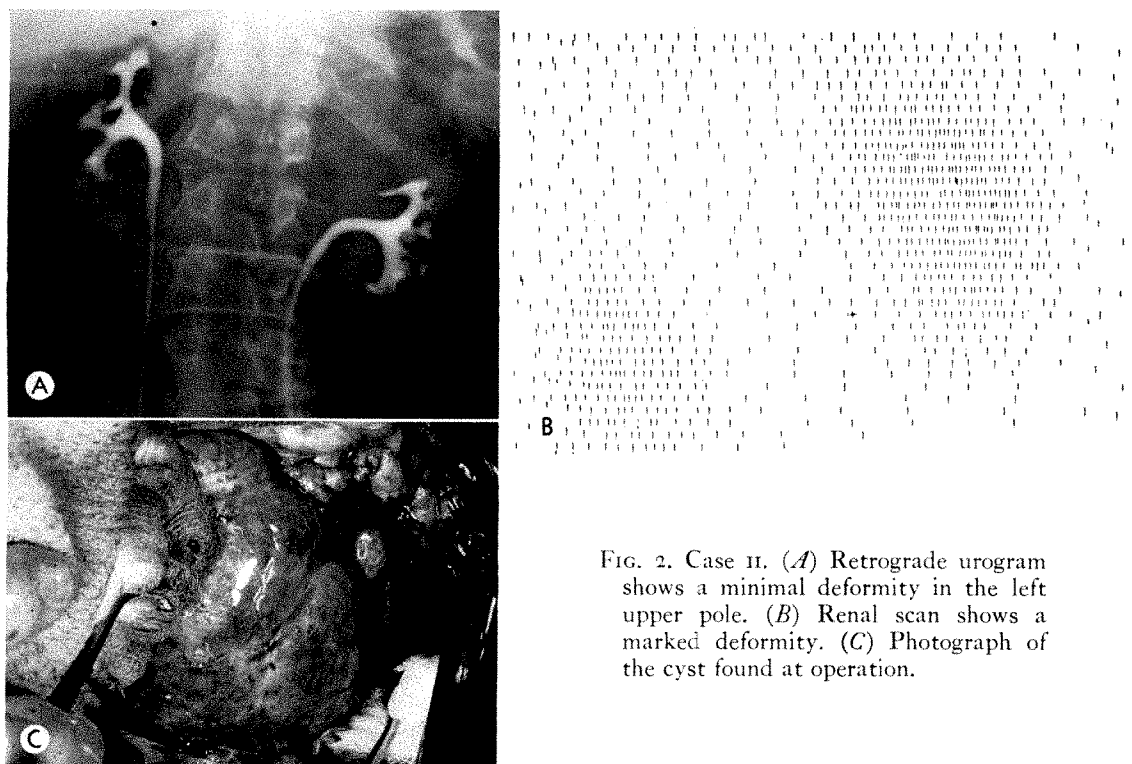


FIG. 2. Case II. (A) Retrograde urogram shows a minimal deformity in the left upper pole. (B) Renal scan shows a marked deformity. (C) Photograph of the cyst found at operation.

pole. Scanning was done during an episode of azotemia and fever which followed the retrograde urographic examination. Subsequent abdominal exploration revealed a renal cyst (Fig. 2C) and hepatic metastatic carcinoma of undetermined origin.

Comment. The scan (Fig. 2B) clearly revealed the absence of I^{131} localization in the left upper pole, together with downward displacement of the left kidney. The parenchymal location of the cyst explains the marked deformity seen on the renal scan and the minimal deformity revealed by retrograde pyelography.

CASE III. A forty-seven year old man with known sickle cell trait was investigated for a solitary episode of painless hematuria. Retrograde pyelography (Fig. 3, A and B) and a renal scan (Fig. 3C) were done. A clinical diagnosis of polycystic disease of the kidneys was made.

Comment. Symmetric defects by I^{131} localization in the lower pole are shown in

the scan; symmetric lesions of the middle calyces are shown on the roentgenograms.

CASE IV. A forty year old man with severe hypertension of 6 years' duration had a bilateral dorsal sympathectomy performed 5½ years before this investigation. Only temporary relief of the hypertension occurred and he was later treated with antihypertensive drugs with minimal results. The intravenous pyelogram (Fig. 4A) showed a large normally functioning right kidney and a small left kidney with decreased function. The aortogram (Fig. 4B), made prior to the renal scan, revealed left renal artery stenosis. The results of split function studies are shown in Table 1. At operation an atherosclerotic plaque was found to be causing the renal artery stenosis. Endarterectomy and dacron patch angioplasty were performed.

Comment. Preoperative renal scan (Fig. 4C) revealed poor I^{131} localization on the left and enlargement of the kidney parenchyma on the right.

CASE V. A thirty-five year old man with diabetes and hypertension was investigated for

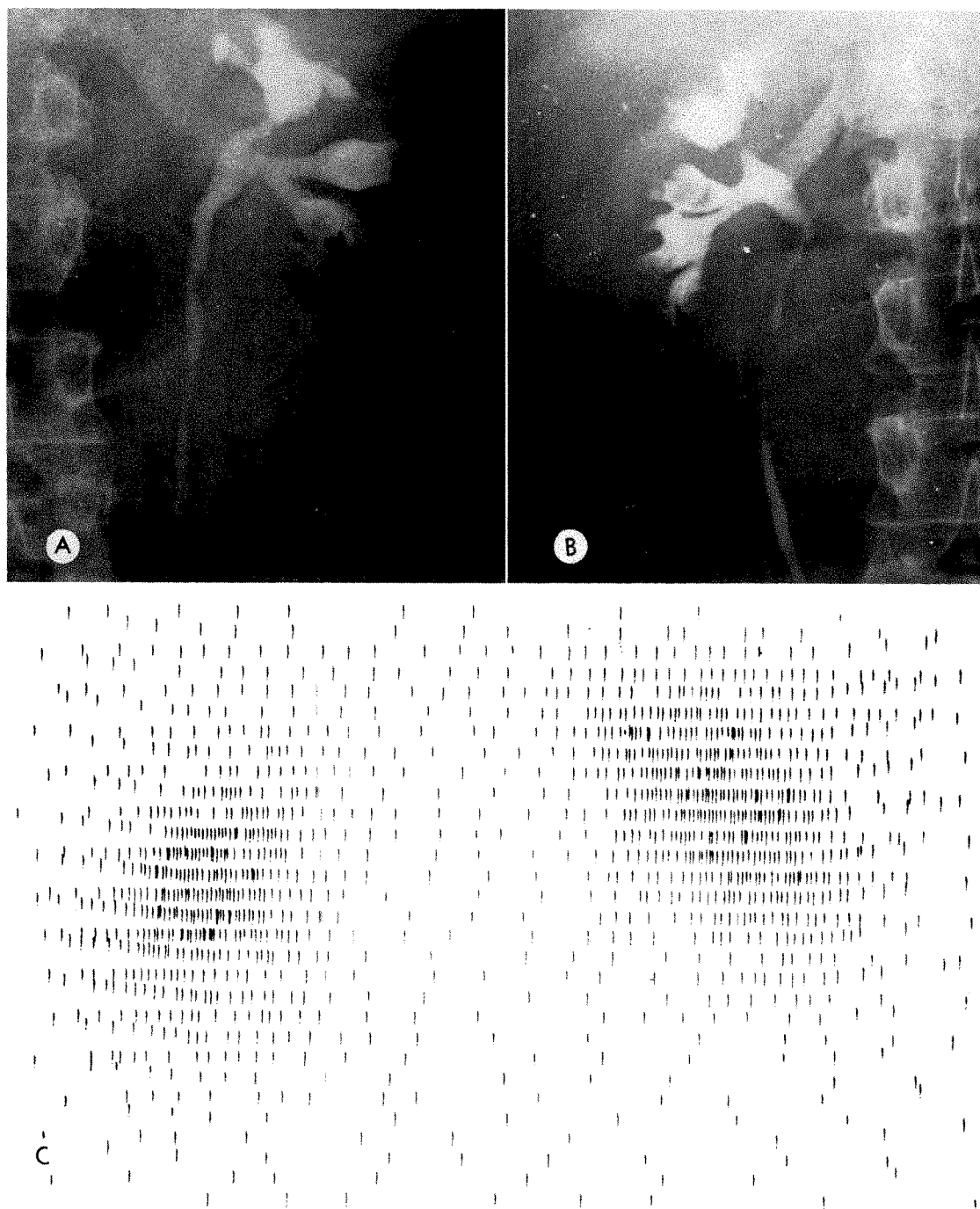


FIG. 3. Case III. (A) Left and (B) right retrograde pyelograms show symmetric lesions of the middle calyces. (C) Renal scan shows symmetric defects in the localization of I^{131} in the lower pole.

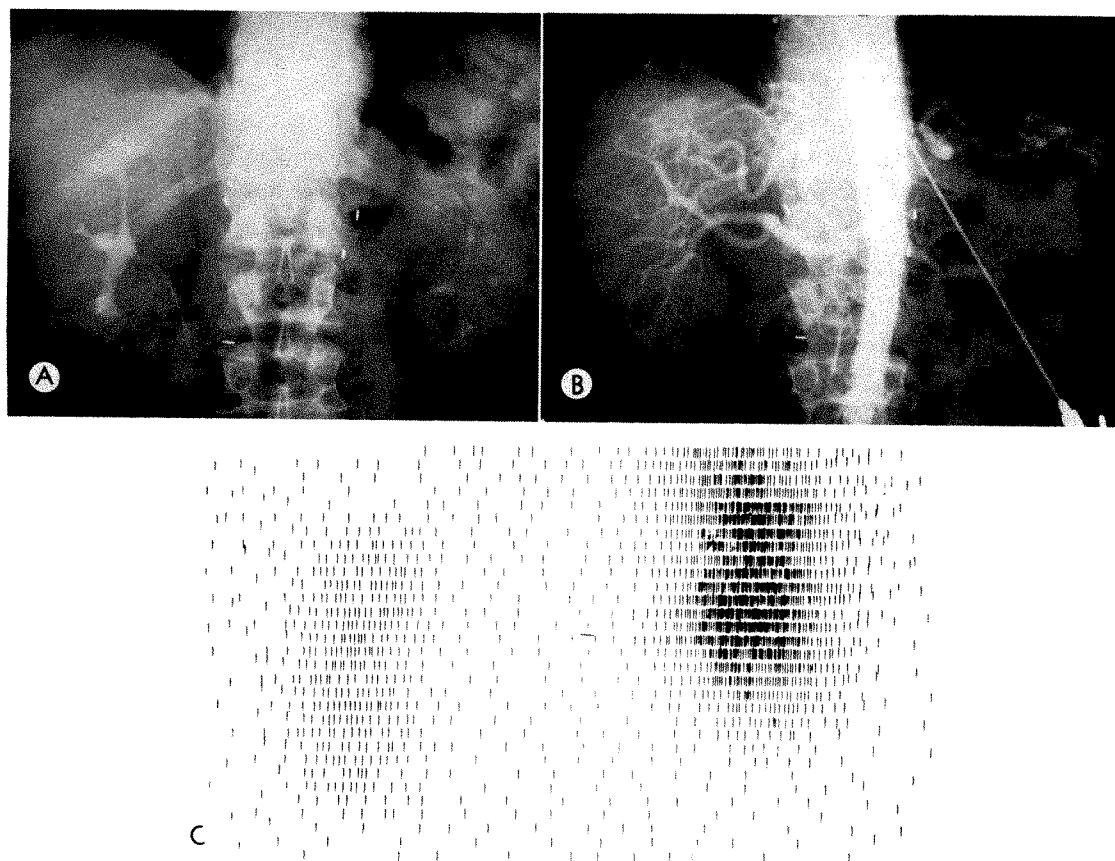


FIG. 4. Case IV. (A) Intravenous pyelogram shows a large normally functioning right kidney and a small left kidney with decreased function. (B) Aortogram reveals left renal artery stenosis. (C) Renal scan shows poor localization of I^{131} on the left and enlargement of the parenchyma on the right.

possible renal lesions. Intravenous pyelography (Fig. 5, A and B) and aortography (Fig. 5C) were done. The renal scan, made before performing aortography, is shown in Figure 5D.

Comment. Lack of arterial supply to the lower pole of the right kidney is seen in both the aortogram and scan. The generalized narrowing of the vascular supply to the left kidney is also confirmed in the scan.

CASE VI. A forty-two year old man with horseshoe kidneys, hypertension of 4 years' duration and blood urea nitrogen of 46 mg. per cent was admitted for control of hypertension. The diagnosis of the congenital anomaly was verified by retrograde pyelography, since no visualization could be obtained by the intravenous technique. A plain roentgenogram of

the abdomen (Fig. 6A) and the renal scan (Fig. 6B) are presented.

Comment. Clear delineation of the abnormality of the axes of the kidneys and lack of function in the midline segment are shown on the renal scan in spite of non-visualization by intravenous techniques.

CASE VII. A thirty-three year old man had three episodes of lumbar pain and microscopically detected pyuria for which short courses of antibiotics were given in the 1½ years prior to this investigation. He had never had fever, hematuria or passage of calculus. During the fourth episode, pain was more severe on the left side. Physical examination was unrevealing and laboratory studies showed normal renal function and a sterile urine culture after antibiotic therapy. Urographic examination (Fig.

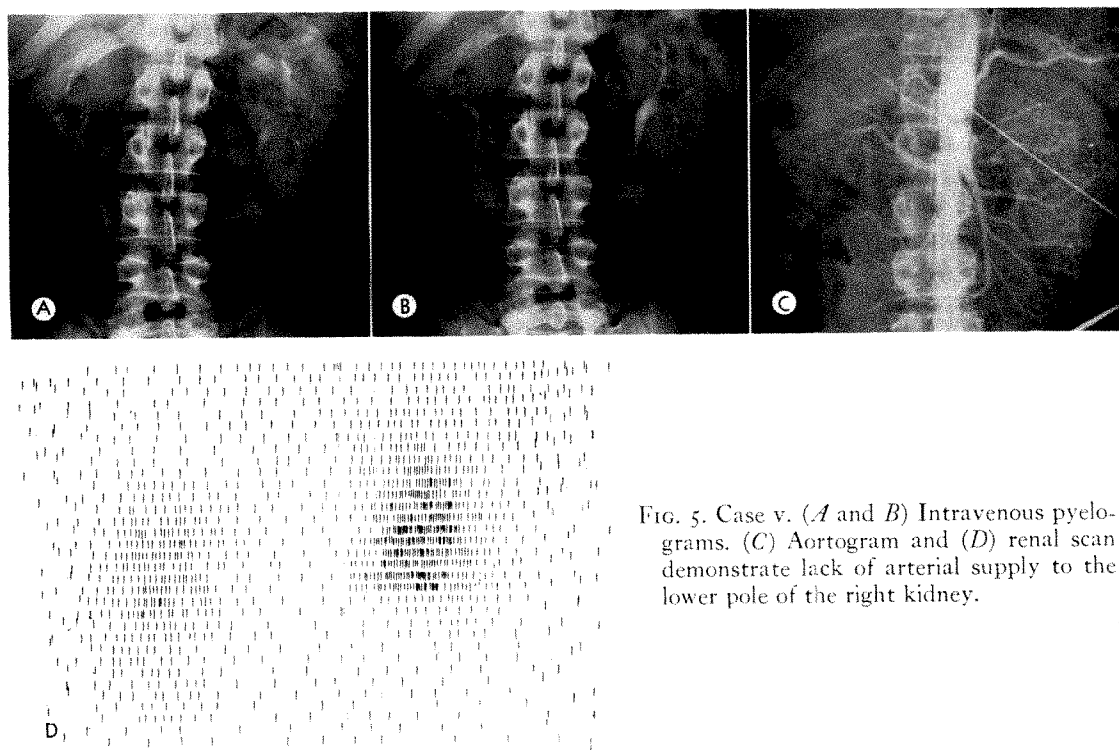


FIG. 5. Case v. (A and B) Intravenous pyelograms. (C) Aortogram and (D) renal scan demonstrate lack of arterial supply to the lower pole of the right kidney.

7A) revealed a nonfunctioning kidney on the left, found to be hydronephrotic by retrograde examination. The scan of the kidneys is shown in Figure 7B. At operation, the hydronephrosis of the left kidney (Fig. 7, C and D) was found to be due to an obstruction at the ureteropelvic junction. The wall of the hydronephrotic sac consisted of a thin layer of renal tissue involved in an acute pyelitic process.

Comment. The scan revealed the lack of significant functioning renal tissue on the left side and the enlargement of the right kidney.

CASE VIII. A forty-four year old man with bilateral hydronephrosis of 7 years' duration was known to have had lower urinary tract obstruction, a right pyeloplasty, and previous pyelonephritis. Intravenous pyelography showed prompt excretion on the left at 3 minutes and excretion on the right at 10 minutes. Neither ureter was visualized until 2 hours after the injection (Fig. 8A). Both kidneys drained completely between 4 and 8 hours. Scans done immediately after injection and at

TABLE I
RESULTS OF SPLIT FUNCTION STUDIES IN CASE IV

	Urine from	
	Right Kidney	Left Kidney
Urine Volume	10.5 ml. 6.8 ml. 6.5 ml.	0.6 ml. 0.6 ml. 0.4 ml.
G.F.R. (Inulin)	95 ml./min. 82 ml./min. 86 ml./min.	10 ml./min. 10 ml./min. 8 ml./min.
R.P.F. (P.A.H.)	465 ml./min. 310 ml./min. 322 ml./min.	63 ml./min. 56 ml./min. 41 ml./min.
Plasma Na	140 mEq./L.	
Plasma Creatinine	1.7 mg. per cent	
Urine Na	139 mEq./L.	87 mEq./L.
Urine Creatinine	79 mg. per cent	180 mg. per cent

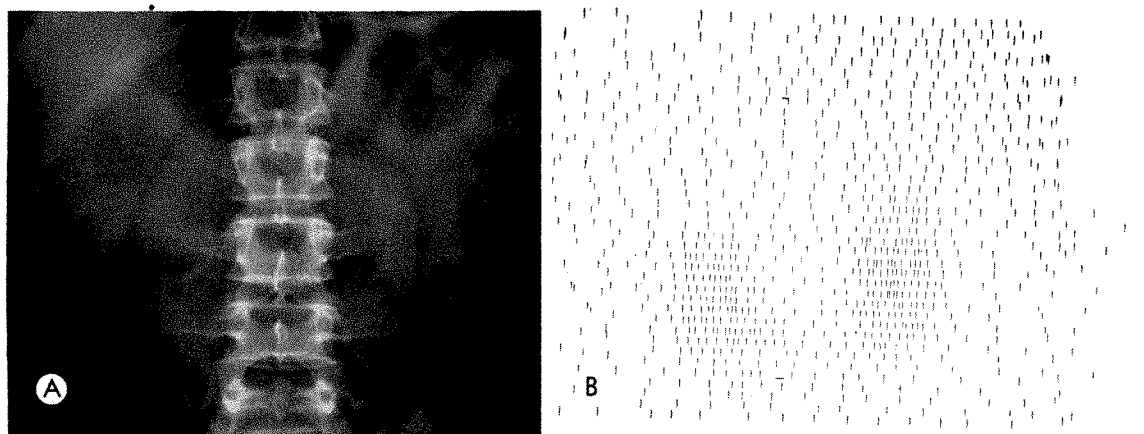


FIG. 6. Case VI. (A) Plain roentgenogram of a patient with horseshoe kidneys. (B) Renal scan demonstrates the abnormality of the axes and lack of function in the midline segment.

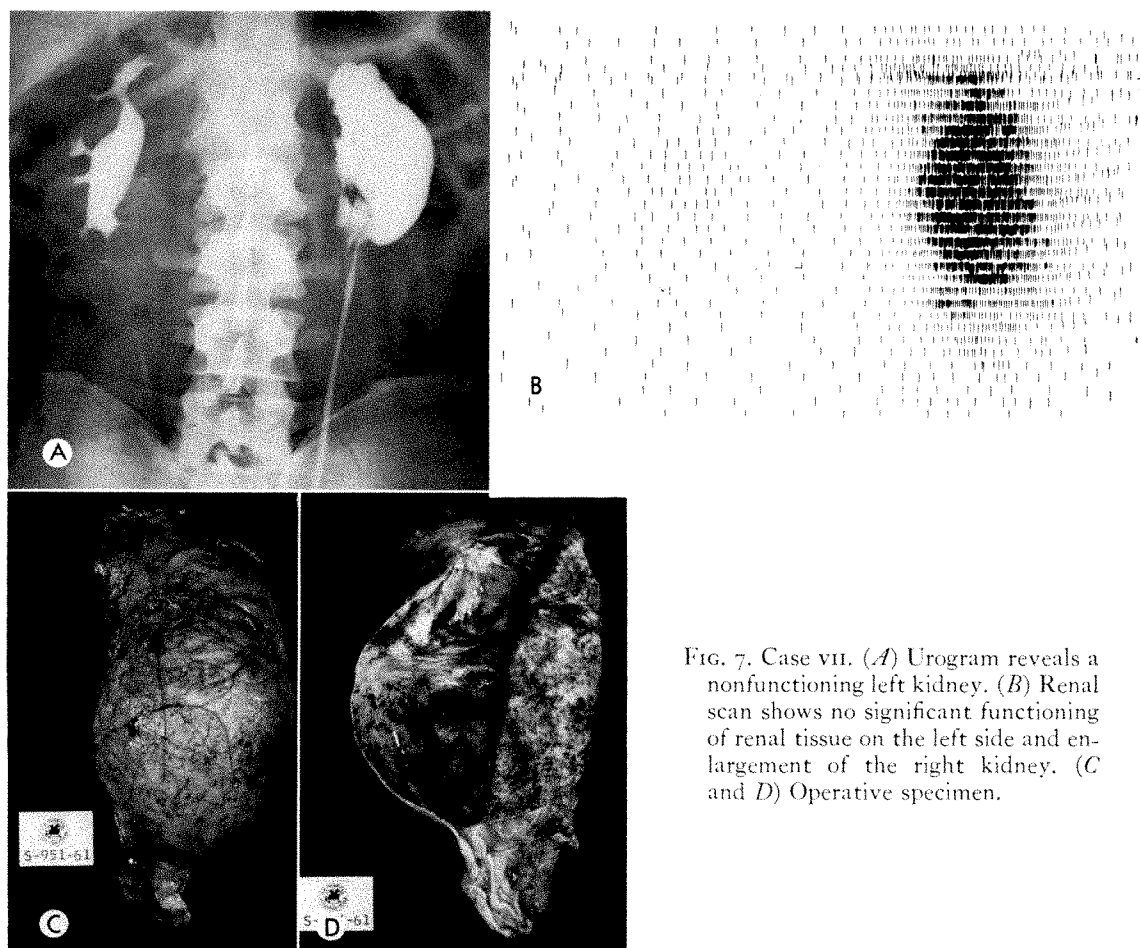


FIG. 7. Case VII. (A) Urogram reveals a nonfunctioning left kidney. (B) Renal scan shows no significant functioning of renal tissue on the left side and enlargement of the right kidney. (C and D) Operative specimen.

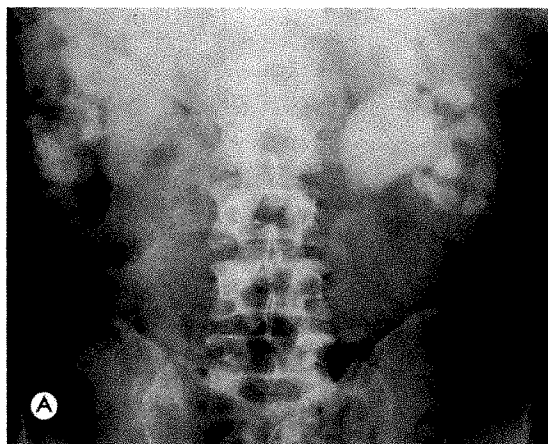


FIG. 8. Case VIII. (A) Intravenous pyelogram, with the ureters first visualized 2 hours after the injection.

30 minutes, $2\frac{1}{2}$ hours, and $5\frac{1}{2}$ hours after injection are shown in Figure 8, B-E.

Comment. The scan done immediately after injection demonstrates good function bilaterally in the presence of severe obstruction of long duration. The serial scans show progressive drainage with complete clearance of the left kidney and significant retention in the right kidney at $5\frac{1}{2}$ hours. To obtain similar information using intravenous pyelographic techniques, the patient would receive at least 4 to 5 times the total body irradiation delivered by the I^{131} during the scanning procedure.

CASE IX. A twenty-five year old man presented with symptoms of lower urinary tract

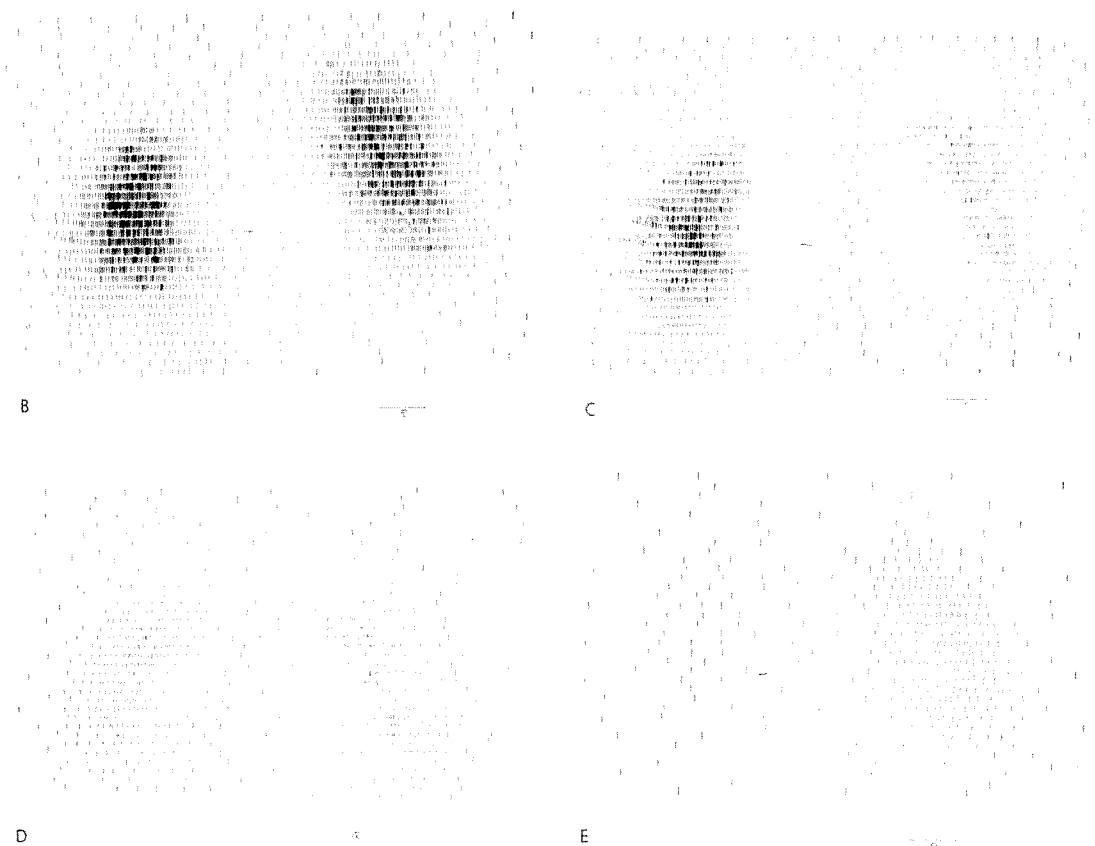


FIG. 8. (B-E) Renal scans immediately after injection and at 30 minutes, $2\frac{1}{2}$ hours and $5\frac{1}{2}$ hours, respectively, show progressive drainage with complete clearance of the left kidney and significant retention in the right kidney at $5\frac{1}{2}$ hours.

obstruction and microscopically evident hematuria. Diagnostic investigation consisted of cystoscopy and panendoscopy as well as bilateral retrograde pyelography. Pre-instrumentation urine culture was sterile and intravenous pyelography was normal. Immediately following instrumentation, the patient's temperature rose to 102°F. Urine and blood cultures revealed growth of *Staphylococcus aureus*. Phenolsulfonphthalein excretion was 20 per cent in 15 minutes. Creatinine was 0.9 mg. per cent. A renal scan was done within 24 hours (Fig. 9A). Chloramphenicol was given for 1 week and a repeat scan was done in 2 weeks (Fig. 9B) when the patient was asymptomatic.

Comment. The initial scan revealed patchy and diminished I^{131} localization throughout both renal areas, but more marked on the left. The scan performed after 2 weeks showed an increase in and greater uniformity of I^{131} concentration.

CASE X. A thirty-four year old woman was admitted for urethral metastatic carcinoma. During hospitalization in the previous year, a Wertheim procedure and cystectomy with ureteral ileal loop diversion were performed for carcinoma of the cervix. Postoperatively, septic left hydronephrosis due to stricture of the left ureter developed, for which an emergency left nephrostomy was done. The stricture was surgically corrected and the nephrostomy tube was removed. Intravenous pyelography (Fig. 10A) done 10 months later shows prompt excretion with no evidence of hydronephrosis. The scan done during this period is shown in Figure 10B.

Comment. The scar of the previous nephrostomy is shown plainly on the scan. Diminished I^{131} localization is seen in the right upper pole and the prompt appearance of I^{131} in the ileal loop is demonstrated.

DISCUSSION

The simplicity and speed of scanning procedures using either diodrast I^{131} or hippuran I^{131} are obvious advantages to both patient and physician. No preparation aside from thyroid protection has been necessary. Preparatory dehydration with

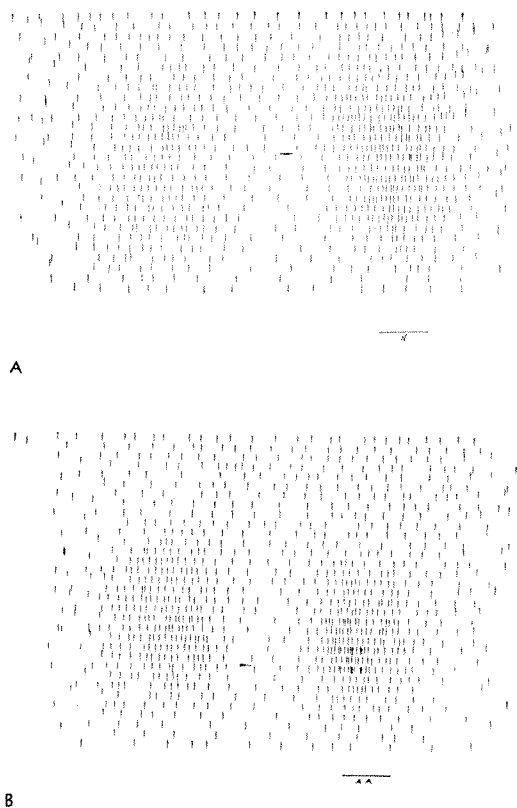


FIG. 9. Case IX. (A) Initial scan and (B) scan made two weeks after A shows the increase in and the greater uniformity of the concentration of I^{131} after the patient had been treated for a staphylococcal infection.

the attendant hazard of nitrogen retention is completely avoided. Intravenous or retrograde pyelography, aortography, or even surgery may be performed during the same day. Repeat scans can be undertaken when desired within 24 hours, due to the rapid excretion of these contrast media. Evaluation is possible in the presence of mild azotemia (blood urea nitrogen in the range of 40 to 70 mg. per cent). Although 600 to 800 μ c I^{131} is administered, retention in the blood with consequent total body and marrow irradiation is small and doses of the order of one-third to one-tenth of those received during roentgen-ray procedures are sustained. Wagner *et al.*⁴ state that when using Hg^{203} - Hg^{205} labeled neohydrin, the radiation exposure is less than 0.5

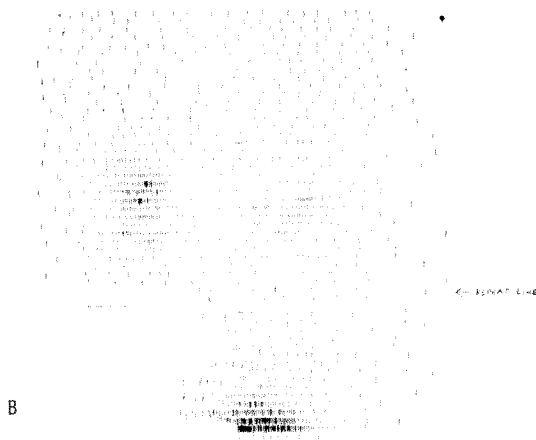
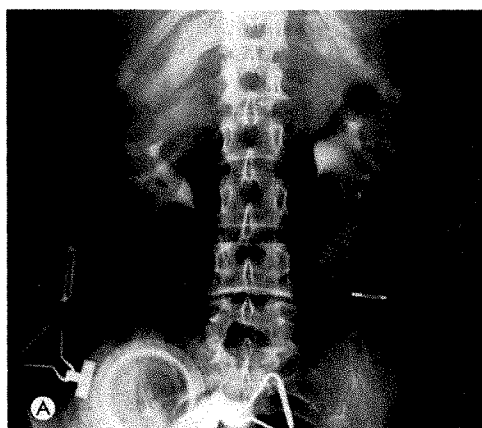


FIG. 10. Case X. (A) Intravenous pyelogram (10 months after left nephrostomy for septic hydronephrosis) shows no evidence of hydronephrosis. (B) Scan shows evidence of the scar from the previous nephrostomy, with diminished localization of I^{131} in the right upper pole and its prompt appearance in the ileal loop.

rad, with the longer retention of labeled diuretics. Our serial studies have resulted in a combined exposure no greater than that from a single intravenous pyelographic examination. The disadvantage of rapid excretion is the absolute necessity for prompt performance of the scanning; if attention is paid in advance to anatomic landmarks, space setting, photopoint setting, etc., no problems are encountered under usual circumstances. The study can be completed in 20 minutes unless, due to an unusual location of the kidneys, each kidney must be studied separately and a second injection has to be done. In addition to minimizing radiation exposure through prompt excretion, the rapid transit of the medium allows one to follow it from the renal parenchyma to the pelvis and to assess drainage of the pelvis in those cases where such information is necessary.

The correlation of the scan and clinical data has been impressive. Abnormalities of scan appearance alone have prompted further fruitful investigation by aortography or split function studies. Thus, on the basis of the present study, renal scanning offers further information and extends data obtained by conventional methods.

SUMMARY

A method of scanning human kidneys has been presented. Illustrative scans are given for patients with tumor deformity, renovascular lesions, infection, hydronephrosis, congenital anomaly and renal injury. The technique offers no significant radiation hazard and appears to be a safe screening method for obtaining information in patients who otherwise would be subjected to aortography and split function studies.

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THE RELATION OF RADIOIODINE DOSIMETRY TO RESULTS AND COMPLICATIONS IN THE TREATMENT OF METASTATIC THYROID CANCER*

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WHEN radioactive iodine first became available as a by-product from the Atomic Energy Commission for use in the study and treatment of thyroid diseases at Memorial Center, a cooperative project, in which representatives from the Departments of Medicine, Pathology, Physics and Surgery participated, was organized to study the possibilities of treating metastatic cancer of the thyroid with radioactive iodine. In the past 12 years this program has been under the direction of the Endocrine Service of the Department of Medicine.

It was well known that most cancers of the thyroid had no function but that an occasional, unusual cancer of the thyroid did acquire function, usually in patients who had been previously thyroidectomized.²¹ The early efforts to treat metastatic cancers of the thyroid with radioactive iodine were characterized by attempts to induce function in such cancers by removal of the normal thyroid,^{18,22} the administration of thyrotropic hormone^{18,22} and periods of treatment with goitrogenic agents such as thiouracil.^{12,17} It was observed that a series of small doses could result in a fatal depression of hematopoiesis. This early experience also showed that metastases treated either with small repeated doses of I¹³¹ or with external irradiation seemed to lose the ability to function but continued to grow.¹⁹

In mid-1949, on the basis of the above observations, it was resolved to treat no metastatic cancers of the thyroid until after the induction of optimum function in

the metastases, and to use the largest dose of radioactive iodine considered safe and therapeutic on the basis of dosimetric studies. In 43 instances between 1949 and 1956 the dose exceeded 200 mc. In 1956, the AEC began to include in the I¹³¹ license a limit of 200 mc on single doses for cancer. Special permission to use larger doses in 10 patients was granted under the Memorial Center license in 1958.

The present paper reports the experience with I¹³¹ in the treatment of thyroid cancer at Memorial Center between October, 1946 and the end of 1960. Many of the patients have been mentioned in prior publications,^{12,15-19,25} but a new attempt at follow-up and a complete recalculation of the dosimetry have been made for each. The reader is referred elsewhere for a review of the historical beginnings of I¹³¹ therapy of thyroid cancer^{21,26} and for recent clinical reports by others.^{4,10,24}

METHODS

Selected patients with histologically proven thyroid cancer who came to Memorial Sloan-Kettering Cancer Center were seen in the Department of Medicine for consideration of radioiodine treatment. Such patients included less than half of all thyroid cancer patients coming to the Center. When possible, diagnostic studies with radioiodine were carried out, using a hand body scan technique and scintigrams, when necessary, either before or after surgery.

In the present report, doses of I¹³¹ given

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to destroy residual normal thyroid tissue in the presence of thyroid cancer, *i.e.*, thyroidectomizing doses, are considered separately from those given to destroy metastases. The latter are designated as cancer therapeutic doses. Thyroidectomy, either by surgery or radioiodine, was nearly always used as the first step in obtaining adequate uptake in metastases.^{18,22} During the period covered, 73 patients received 81 thyroidectomizing doses of I^{131} for thyroid cancer. Six patients received 2 doses and 1 had 3 doses to hasten the thyroidectomy because of a pressing clinical situation. The average thyroidectomizing dose was 67 mc, but in recent years an arbitrarily selected dose of either 75 or 100 mc has been used routinely to ablate the normal thyroid. Tracer studies but no dosimetric studies were performed before the thyroidectomizing dose was given, and measurements after such treatments were often limited to a 24 or 48 hour thyroid uptake.

Cancer therapeutic doses were subsequently given to 26 of the 73 radioiodine-thyroidectomized patients. Of all the patients receiving cancer therapeutic doses of I^{131} , 28 had had "total" surgical thyroidectomy. Radioiodine was required to complete the thyroidectomy in 4 of these cases. Only 5 patients received cancer therapeutic doses without a previous attempt at thyroid ablation. In general, cancer therapeutic doses were given only when tumor uptake was demonstrated by external counting.

For the present paper, a review was made of the medical and isotope laboratory records of 59 patients who received 122 doses of I^{131} in the treatment of metastatic cancer. All cancer therapeutic doses of radioiodine, as defined above, have been included in this report. Follow-up contact with patients was obtained between December, 1959 and January, 1961 when possible. Fifteen patients who received 23 treatments with I^{131} at the Brookhaven National Laboratory, Upton, Long Island, between December, 1949 and August, 1954

are also included through the cooperation of those responsible for their care.* All of these 15 patients came originally to our institution and while at Brookhaven were seen once each week by members of the Memorial group. They had radioiodine tracer studies and most had I^{131} treatments at Memorial Center in addition to the treatments at Brookhaven.

Where basic laboratory data met certain defined criteria of completeness, the radiation dose predicted or observed was recalculated, applying uniform methods. The minimum data required were at least 5 determinations of whole blood I^{131} during a minimum of 6 days to estimate the beta ray (β) dose to blood, and at least 5 days of consecutive complete collections of urine following administration of I^{131} to estimate the gamma ray (γ) dose. The usual program included a measurement of whole blood I^{131} at 4 hours and each day thereafter, counting of the principal loci of concentration of radioactivity in the body every day except on weekends, and measuring total urinary I^{131} daily. The whole study usually lasted 8 days. Some treatments were studied in such a manner for intervals exceeding 30 days.

The beta ray dose was estimated from a plot of the logarithm of the per cent of dose per liter of whole blood versus days, with a method modified from Berman, Rall and Heslin,¹ using semilogarithmic paper with a suitable number of decades (Fig. 1). A straight line was fitted to the final phase and extrapolated to zero time. The difference between this line and each point of the data not fitting the line was then replotted, using distinctive symbols. A second straight line was next fitted to these points of differ-

* We wish to acknowledge the assistance of Dr. Charles G. Lewallen, presently of the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, in furnishing laboratory data on several patients, and the permission of Drs. Lee E. Farr and Lewis K. Dahl to review clinical records at Brookhaven. One patient, R.T., with a Hürthle cell cancer, was treated at Brookhaven and subsequently died of acute myelogenous leukemia. She had been excluded from the report, since Dr. Lewallen is reporting the case elsewhere.

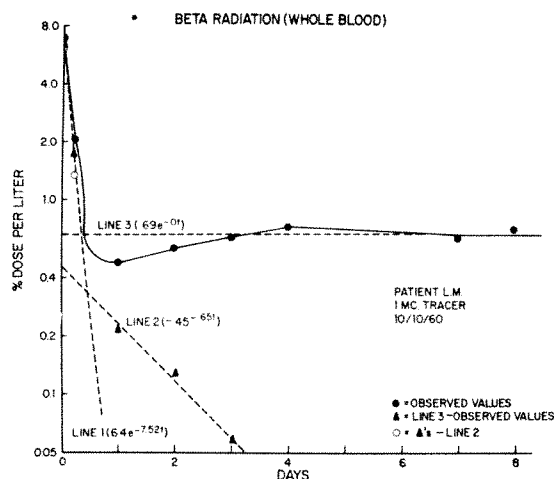


FIG. 1.

ence and extrapolated to zero time. When further differences remained, a third fit was required. The observed data then described a line (m_i) of the shape

$$m_i = \sum A_1 e^{-K_1 t} + A_2 e^{-K_2 t} + \dots + A_i e^{-K_i t}$$

where A represents the intercept in per cent of dose per liter, K the slope of the linear fit in fraction per day and t the time in days after the dose. The signs of the components were determined by increasing or decreasing rates. The area under this line is the summation of the fractions A/K . To correct for physical decay, the fractional decay constant for I^{131} (0.0866 per day) was added to the values of K . The area (M_i) under the whole blood curve from time zero to infinity is

$$M_i = \sum \frac{A_1}{K_1 + 0.0866} + \frac{A_2}{K_2 + 0.0866} + \dots + \frac{A_i}{K_i + 0.0866}$$

per cent dose days per liter.

For a dose of 1 mc, $M_i/100$ is the mc-days per liter. On the basis of an average β energy of 0.187 mev.⁹ for I^{131} and allowing for complete absorption of the β dose in blood, 1 mc-day per liter delivers 10 rads from β . Letting Mc represent the millicuries administered, the β dose to whole blood is

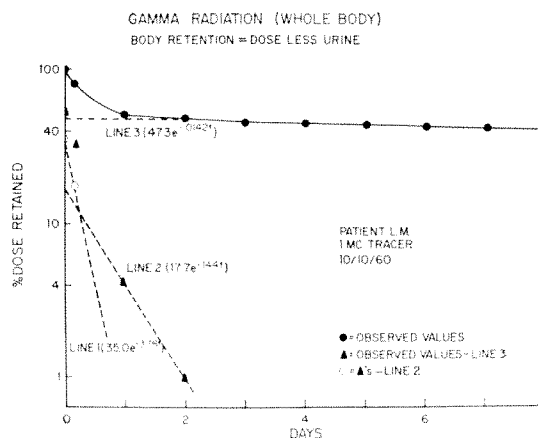


FIG. 2.

$$D_\beta = \frac{10 Mc M_i}{100} = \frac{Mc M_i}{10} \text{ rads.}$$

This method was used for both the tracer and therapy data, using the mc in the dose with the M_i for the tracer to calculate the predicted dose and with the M_i for the treatment to calculate the observed dose.

The contribution of gamma ray to the whole blood total radiation was estimated from a similar plot of the log of the per cent dose retained (100 - cumulated per cent in urine) versus days (Fig. 2). The data were fitted with a series of exponentials describing a curve

$$m_b v_b = A_1 e^{-K_1 t} + A_2 e^{-K_2 t} + \dots + A_i e^{-K_i t}$$

where m_b is a metabolizing function of iodine and v_b is the body weight.

The area ($M_b V_b$) under the curve, similarly, is

$$M_b V_b = \sum \frac{A_1}{K_1 + 0.0866} + \frac{A_2}{K_2 + 0.0866} + \dots + \frac{A_i}{K_i + 0.0866}$$

per cent dose days for the whole body, where M_b is a function of dose and V_b is body weight in kilograms.

For a dose of 1 mc, $M_b V_b/100$ is the mc-days for the whole body. Taking the point

source γ dose rate constant, Γ , for I^{131} at 2.18 rads per mc-hour (equivalent to an average γ energy of .397 mev.)[†] and omitting the effect of incomplete absorption, there are 20.4 rads from γ radiation for each mc-day per kilogram. Absorption of γ radiation is incomplete, however, and is a complex function of the size and shape of the body containing the emitter, its distribution and the locus of the critical organ. For the estimates used here, 0.4 was taken as the fraction of the γ radiation affecting the blood. This corresponds to an average geometric factor (\bar{g}) of 156,⁹ which would correspond to a man 140 cm. tall and weighing 100 kg.³ Thus the γ dose from Mc millicuries is

$$D_{\gamma} = \frac{M_b V_b \times Mc \times 0.4 \times 20.4}{100 V_b}$$

where V_b = body weight in kilograms. Blood β and γ radiation doses were added to obtain the blood total radiation predicted or observed.

Dose size was selected, for many patients in the series, to deliver 300 rads to the blood. This dose was intended to give the largest amount of I^{131} which the patient could tolerate in relative safety. A dose which would deliver less than 300 rads was used when the disease was less threatening. Estimation of tumor dose was usually not attempted because of variable and unknown geometric factors which complicated such estimates.^{14,25} Doses were further restricted with regard to the mc retained at 48 hours (per cent retained at 48 hours $\times 0.841 \times Mc$) in order not to exceed 138 mc¹⁶ or, in the case of diffuse pulmonary metastases, not to exceed 80 mc.^{15,25}

Resulting radiation complications were graded on the basis of 5 groups as follows: 0 = none; 1 = detectable; 2 = moderate; 3

= severe; and 4 = fatal. When bone marrow suppression was the complication observed, a detectable complication was defined as a depression from normal levels of platelets to less than 100,000 per cu. mm., hemoglobin below 10 gm. per 100 ml., or white blood cell count below 3,000 per cu. mm. during the first month after treatment. A depression sufficient to require multiple transfusions was considered severe. When radiation pneumonitis was accompanied by persistent dyspnea, the complication was called severe. Deaths from infection in the presence of bone marrow depression were counted as radiation deaths. The term "serious complication" was used to include the severe and fatal groups.

Beneficial results were defined to include only objective changes such as decrease in size of tumors noted by palpation or roentgen examination. A good result which was reversed before one year after treatment or which was nullified by the growth of another lesion or death of the patient was called temporary. Survival figures were based on length of life after histologic diagnosis until death, loss to observation or the end of 1960 if the patient was known to be alive any time in 1960.

RESULTS

Table 1 compares the incidence of the various histologic types in all thyroid cancer patients with this diagnosis seen at Memorial Center during a 25 year period^{8,13} with the incidence of the various types in patients treated with I^{131} during an overlapping 14 year interval. The table shows a significantly higher incidence of follicular and alveolar type tumors in the radioiodine series. No patients with Hürthle cell* or giant and spindle cell cancer were treated with I^{131} .

A. STIMULATION OF UPTAKE

Various methods were used to induce increased concentration of radioiodine in metastases. Thyroidectomy, antithyroid agents or TSH injections were used alone or in combination in many patients. Since

[†] Prior to January 1, 1955, the millicurie dosages at Memorial Center were based on a Γ of 2.64 rads/mc-hour,^{11,6} the standard being the New York millicurie. Since that time the National Bureau of Standards (NBS) millicurie has been used, with a Γ of 2.18.⁹ Thus 1.2 NBS mc equals 1 New York mc. Publications from Memorial Center prior to 1957 reported studies using the larger millicurie. All data in this paper are corrected to the NBS millicurie, which is now in general use.

TABLE I
INCIDENCE AND SURVIVAL BY HISTOLOGIC TYPE

Histologic Type	All Thyroid Cancer Cases at Memorial Center—1930-1954*			Radioiodine Treated—1946-1960		
	No. of Cases	Per Cent	Five Year Survival (per cent)	No. of Cases	Per Cent	Five Year Survival (per cent)
Papillary	393	56	68	28	47	75
Follicular and Alveolar	80	11	61	22	37	40
Solid	85	12	24	8	14	25
Hürthle Cell	62	6	60	0	0	—
Giant and Spindle Cell	45	9	0	0	0	—
Unclassified	40	6	22	1	2	100
Total	705		60	59		54

* The papillary cases are from Frazell and Foote⁸ and the other cases are from Oroppeza and Frazell.¹²

this series is limited to patients treated with I^{131} , comparisons of these methods of stimulation have not been made. Some observations comparing the dosimetry for tracer and therapeutic radioiodine in relation to the methods of stimulation were possible, and are reported here together with certain side effects of the stimulation.

Antithyroid agents were administered within a month and then withdrawn before 60 of the treatments in an attempt to stimulate the uptake. If a course of antithyroid agents was used to stimulate the uptake of a tracer, it proved desirable to administer another course immediately before the therapy. In 23 instances, when antithyroid drugs were given before the tracer but not before the therapy, the 48 hour retention of the I^{131} therapy dose averaged 72 per cent of the predicted retention with a standard error of the mean of 6 per cent, a highly significant decrease from the prediction. In 19 instances, when the drugs were given between the tracer and the therapy doses, the retention was 96 ± 8 per cent of that predicted. Thus, failure to administer antithyroid agents between the tracer and the therapy doses caused a difference in retention which was significant at the $p=0.01$ level.

Myxedema, as manifest clinically or by a low serum protein bound iodine (PBI), was seen prior to the administration of 33 can-

cer therapeutic doses as the result of thyroidectomy with or without the use of antithyroid agents. One patient who received a cancer therapeutic dose was observed to develop a myxedema psychosis after thyroidectomy and during the prolonged administration of thiouracil. Three of the patients were thyrotoxic from functioning metastatic tumor prior to treatment.

Stimulation of tumor function by the injection of heterologous thyroid stimulating hormone (TSH) was attempted prior to 8 pre-therapy tracer doses and 7 therapeutic doses,^{4,18,22} but in only 4 cases was TSH given prior to both the tracer and the therapy doses. In these 4 cases the 48 hour retention of I^{131} was 75 per cent of that predicted. Sensitivity manifest by urticaria necessitated stopping the TSH in 1 patient.

The problem of increased tumor growth during stimulation procedures^{4,5,10} could not be adequately evaluated from this retrospective study, but such growth has not been obvious or troublesome. Moreover, the growth of metastases in many patients has not been prevented by the administration of more than adequate replacement doses of thyroid hormones or their analogues.

B. PREDICTABILITY

The ability to predict from a prior tracer study the radiation dose to be delivered by

TABLE II
PREDICTABILITY OF RADIATION DOSE

Type of Estimate	No. of Paired Estimates	Per Cent of Predicted Radiation Observed*	Significance of Predicted vs. Observed (p)	Correlation Coefficient* (r)	Significance of Correlation (p)
Blood Total Radiation	41	79 ± 5	< .001	.55 ± .01	< .01
Beta Radiation (of blood)	55	115 ± 12	> .1	.23 ± .07	.02
Gamma Radiation (whole body)	55	73 ± 5	< .001	.46 ± .01	< .01
Millicuries Retained at 48 Hours	84	87 ± 4	< .001	.66 ± .06	< .001

* With the standard error.

the treatment is shown in Table II. Considerable variability occurred. The observed blood total radiation ranged from 34 to 153 per cent of the expected value. Body retention varied from 22 to 217 per cent of expected. The average values for the total radiation delivered to the blood, the γ dose and the millicuries retained at 48 hours were significantly less than predicted, whereas the β radiation was not significantly less. Correlation between the tracer and the therapy doses, although significant for each type of estimate, was not high.

C. RADIATION DOSES

The 122 doses ranged in size from 6 to 600 mc and averaged 194 mc. They exceeded 200 mc in 52 instances, including 9 larger doses in 8 patients treated since 1958 by special arrangement with the AEC licensing branch, as indicated above.

Adequate data to calculate the blood total radiation were available for 85 treatments. The whole blood radiation dose ranged from 45 to 740 rads, with a mean of 267 rads. The largest single dose in millicuries was 600, delivering 250 rads and producing a retention of 79 mc at 48 hours. The largest blood total radiation from a single dose was 740 rads from 503 mc, with a retention of 135 mc at 48 hours. Three patients in the series received cumulative total doses of I^{131} between 885 and 1,030 mc, exclusive of tracer doses, which delivered between 700 and 1,100 rads of blood total radiation. Smaller numbers of millicuries often delivered larger amounts of

blood total radiation (*cf.* patients G.T. and I.M., Table III). The 85 doses delivered to blood a mean of 1.15 rads per mc, with a standard error of 0.06. The range of rads per mc was from 0.31 to 3.21. By the method used, beta radiation averaged 56.4 ± 1.7 per cent of the blood total radiation in these doses.

D. RADIATION COMPLICATIONS

Side effects of irradiation were observed following administration of two-thirds of the therapeutic doses. Nausea was the most frequent, occurring after 44 treatments and accompanied by vomiting in 30 instances. Bone marrow depression was the next most frequent complication, occurring in 38 instances. Other complications, graded detectable or moderate, and the frequency, if observed more than once, were pain in tumor (8), parotitis (3), unpleasant taste (3), dry mouth (2), sore mouth, diarrhea, redness of the skin over metastases, thrombophlebitis of a leg, alopecia over metastases and aspermia. The PBI increased more than 2 μ g. per 100 ml. in 6 of 11 patients in whom it was measured during the first weeks after treatment, but was not usually associated with signs of thyrotoxicosis.

Serious side effects, including both severe nonfatal and fatal radiation complications, occurred after 14 treatments. Serious bone marrow depression was observed 8 times, radiation pneumonitis resulted 5 times and vomiting persistent for 30 days was seen once (Table III). Table IV shows that serious

TABLE III

THE DOSE IN PATIENTS DEVELOPING SERIOUS RADIATION COMPLICATIONS

Patient	Site of Metastasis	Dose (mc)		Blood Total Radiation (rads)		mc Retained at 48 Hours	Complication Type	Severity
		Last	Cumulative	Last	Cumulative	Last Dose		
P.G.	Bone	300	630	433	640	151	Marrow depression	4
M.A.	Bone	184	1,030	213	1,100	54	Marrow depression	4
O.D.	Lung	212	290	363	—	150	Pneumonitis	4
G.F.	Lung	300	390	488	—	176	Pneumonitis	4
G.T.	Bone	600	660	250	—	79	Marrow depression	3
F.K.	Bone	377	950	227	840	116	Marrow depression	3
J.M.	Bone	324	550	170	300	81	Marrow depression	3
J.D. 1st	Bone and lung	209	210	206	—	47	Marrow depression	3
J.D. 2nd	Bone and lung	302	510	312	520	119	Marrow depression	3
I.M.	Bone and lung	209	450	582	960	151	Marrow depression	3
P.L.	Lung	362	660	292	780	86	Pneumonitis	3
D.K.	Lung	289	885	252	700	68	Pneumonitis	3
L.F.	Lung	351	442	650	—	236	Pneumonitis	3
L.P.	Bone	240	370	—	—	155	Vomiting	3

radiation complications were more frequent when the dose exceeded 300 mc, occurring with 28 per cent of such doses as compared with 6 per cent of doses less than 300 mc and with only 1.5 per cent of doses less than 200 mc. These differences were statistically significant ($p < 0.01$) using a chi-square test. Serious complications were also more frequent when the blood total radiation exceeded 200 rads, being observed after 21 per cent of such doses, as compared with 3 per cent following amounts of radiation

smaller than 200 rads to the blood (Table v). This difference was significant at the level of $p = 0.03$. A significant increase in serious side effects was also associated with the retention of over 150 mc in the body at 48 hours after administration of the dose (Table vi). The increased risk was associated both with the predicted and the observed retention, although these were not always identical in value. In 7 of the 14 treatments in which serious radiation complications were observed (Table iii) blood

TABLE IV

COMPLICATIONS AND RESULTS IN RELATION TO MILLICURIES GIVEN

Millicuries Administered	No. of Doses	Serious Radiation Complications			Objective Good Results		
		Severe	Fatal	Total (per cent)	Sustained	Temporary	Total (per cent)
0-99	30	0	0	0	1	3	13
100-199	37	0	1	3	12	8	54
200-299	26	4	1	19	4	6	38
300-399	24	5	2	29	4	4	33
Over 400	5	1	0	20	0	1	20
Total	122	10	4	11	21	22	35

TABLE V
COMPLICATIONS AND RESULTS IN RELATION TO BLOOD TOTAL RADIATION

Blood Total Radiation (rads)	No. of Doses	Serious Radiation Complications*			Objective Good Results*		
		Severe	Fatal	Total (per cent)	Sustained	Temporary	Total (per cent)
0-99	5	0	0	0	1	1	40
100-199	24	1	0	4	7	6	54
200-299	33	5	1	18	7	3	30
300-399	7	1	1	29	1	2	43
400-499	9	0	2	22	2	1	33
Over 500	7	2	0	29	1	2	43
Unknown	37	1	0	3	2	7	24
Total	122	10	4	11	21	22	35

* See text for definition of classification.

total radiation was less than 300 rads and body retention was less than 120 mc at 48 hours, the limits which have recently been observed at Memorial Center.

Fatal complications occurred in 4 patients, or following 3 per cent of the treatment doses. Two patients died of bone marrow depression and sepsis 5 and 13 weeks after the last dose of I^{131} . Two patients died of radiation pneumonitis. They were reported in detail by Rall and his co-workers.¹⁵ There have been no fatalities since 1954 when restrictions concerning millicuries retained at 48 hours were adopted.

TABLE VI
THE RELATIONSHIP BETWEEN SERIOUS COMPLICATIONS AND MILLICURIES RETAINED

Millicuries Retained at 48 Hours	Predicted		Observed	
	No. of Doses	Serious Complications (per cent)	No. of Doses	Serious Complications (per cent)
0-49	15	0	35	3
50-99	36	6	38	13
100-149	28	16	20	10
150 and over	11	55	12	50
Unknown	32	6	17	0
Total	122	11	122	11

E. REMISSIONS

Objective beneficial effects occurred following 43, or 35 per cent, of the treatments. Good effects were observed in 27 of the 59 patients. The distribution of these results between sustained and temporary remissions is shown in Table VII. The highest incidence of good results followed doses ranging in size from 100 to 200 mc (Table IV), and doses of this size or larger gave significantly more remissions than lower doses. Although doses delivering between 100 and 200 rads of blood total radiation showed the best results, the difference between the remission rate for this amount of blood radiation and that for larger or smaller amounts was not statistically significant (Table V). Remissions could not be related to the millicuries retained at 48 hours.

Sustained objective remissions occurred in 12 patients with pulmonary metastases, in 2 with skeletal metastases and in 2 with inoperable, metastatic lymph nodes in the neck. Temporary remissions were manifest by decrease in the size of lung lesions seen roentgenographically in 4 patients, by shrinkage of palpable masses arising in bones in 5 patients and by objective recovery of nerve function in 2 patients. Lung metastases occurring as the only detected involvement were most susceptible to treatment, responding in 11 of 14 cases.

TABLE VII
THE RESULTS OF TREATMENT OF THYROID
CANCER WITH I^{131}

Results	Doses		Patients*	
	No.	Per Cent	No.	Per Cent
Sustained Objective Remission	21	17	16	27
Temporary Objective Remission	22	18	11	19
Too Early to Evaluate	7	6	5	8
No Information	4	3	3	5
No Effect	68	56	24	41
Total	122		59	

* Classified only in the first applicable group.

Neck lymph node and mediastinal metastases were less susceptible, with good responses in 2 of 11 cases. Patients with bone metastases and multiple types of involvement constituted a middle group with remissions in 5 of 14 and 9 of 20, respectively.

The survival rate of patients treated with radioiodine was no better than the survival rate of those treated by other methods. Table I compares the 5 year survival percentage for all patients with thyroid cancer seen at Memorial Center in the years 1930-1954^{8,13} with the 1946-1960 radioiodine series. The survival rate for the follicular and alveolar type of thyroid cancer appeared less when radioiodine was used, but the difference was not statistically significant.

DISCUSSION

The histologic structure of the cancer as seen in the available tissue sections proved to be one of the most reliable criteria as to whether or not the patient could be treated with I^{131} . Since significant uptake of I^{131} was required before treatment could be given, the relatively higher incidence of follicular and alveolar carcinoma in the radioiodine series reflects the greater likelihood of metastases of this type to function. This confirms the autoradiographic data of Fitzgerald *et al.*⁷ Although stimulation of the ability of the tumor to concentrate

radioiodine has been attempted in patients with Hürthle cell and giant and spindle cell types of cancer, the absence of such patients from this series suggests that these types rarely, if ever, function enough to permit radioiodine therapy.

It is apparent that the initial approach to the treatment of thyroid cancer should be surgical in order to make a diagnosis, to determine the histologic type and to completely excise the disease whenever possible. Radical surgery probably offers patients the best chance for cure when the disease has not metastasized beyond the neck. Because of the risk of parathyroid insufficiency, as indicated by Black *et al.*,² the recommendation of total thyroidectomy at the time of the original operation is made less often now. Total surgical thyroidectomy, moreover, has sometimes left normal thyroid tissue which required subsequent thyroidectomizing doses of radioiodine. In the presence of distant metastases, biopsy only may be sufficient if followed by a radioiodine thyroidectomy.

Because of the complex geometric interrelationships between areas of assorted concentrations of radioiodine and the critical organ for radiation damage, estimates of dose from γ radiation are subject to marked error. Estimation of bone marrow dose is especially difficult in patients with functioning metastases which may be either near to or far from active marrow. Such geometric differences are probably also important in lung tissue involved with either diffuse or discrete metastases. Assuming that as much as 0.4 of the total γ energy is absorbed, as it might be under conditions of uniform distribution in a heavy, short patient as described under "Methods" above, the error should be toward the side of safety. Rall and co-workers¹⁶ found that a factor of 0.09 enabled them to relate radiation dose to the fall in total lymphocyte count most closely. The 0.4 used in the present method should constitute a safety factor of 4 times, but even such a factor may have been entirely nullified by considerations of tumor-sensitive area geometry.

The treatments, on the average, failed to deliver the radiation doses to blood that were predicted, except in the case of β radiation. This decrease must have been in large part due to more rapid excretion of the treatment dose as a result of radiation effects on mechanisms which hold the I^{131} in the body. The failure to observe this difference for the β dose to blood may well have been due to a release of thyroglobulin from the tumor into the blood in some patients as a result of radiation, as reported by Robbins and colleagues,²⁰ and interpreted by Rall and co-workers.¹⁶ The lesser difference in body retention figures at 48 hours (Table II) as compared with the γ dose, which is an estimate for a longer period of time, would also suggest a greater effect with passing time, compatible with a radiation mechanism.

Predictability was not improved if doses resulting in the retention of more than 138 mc were excluded, as has been previously reported.¹⁶ The retention of more than this amount was associated with an observed blood total radiation of more than 120 per cent of that predicted in only 3 of 10 treatments with high 48 hour retention. Conversely, in 4 treatments which delivered more than 120 per cent of the expected blood radiation, only 2 were associated with retention of more than 138 mc (Table VIII). Moreover, the prior tracer study failed to predict this retention in any of these 4 treatments. Radiation complications, on the other hand, were more frequent if the radioiodine retained at 48 hours exceeded 150 mc (Table VI).

The radiation dose calculated from the observed blood and body retention data depends in some measure on the method of estimation. Values such as the per cent of the blood total radiation due to β radiation may have been strongly influenced by the method used, since various assumptions about γ contribution have been made by different observers. The value of 56 per cent from β obtained here compares with values of 53 and 75 per cent calculated from the assumptions of Rawson *et al.*¹⁹ and Seidlin and co-workers,²³ respectively. The rads to

TABLE VIII
DATA FOR 4 DOSES WHICH DELIVERED OVER 120
PER CENT OF PREDICTED BLOOD TOTAL
RADIATION

Patient	Milli- curies Admin- istered	Blood Total Radiation (rads)		Millicuries Retained in Body at 48 Hours	
		Pre- dicted	Ob- served	Pre- dicted	Ob- served
L.F.	351	495	650	118	236
O.S.	329	259	366	100	130
S.C.	427	360	515	95	180
M.T.	350	277	425	111	133

blood per millicurie of dose extended over a wide range, as would be expected in a group of patients with considerable variation in the metabolism of iodine. The mean of 1.15 rads per millicurie agrees well with a value of 1.2 rads per millicurie calculated by Loevinger and co-workers⁹ from representative data for a hyperthyroid patient with an uptake of 75 per cent.

An 11 per cent incidence of serious radiation complications is perhaps acceptable in dealing with a malignant disease. With regard to radiation deaths, 3 per cent (of doses) or 7 per cent (of patients) certainly is not an acceptable risk for such treatment. Perhaps 2 or 3 of the fatal complications and 3 of the nonfatal complications could have been avoided if presently followed restrictions on dose had been observed. Doses now are planned to limit blood total radiation to 200 rads except in certain clinical emergencies, and body retention, in the absence of diffuse lung metastases, to 120 mc, whichever is more limiting. In the presence of functioning, diffuse lung metastases, retention is limited to 80 mc.^{15,25} These limitations on body retention at 48 hours, in use since 1954, have so far prevented fatal complications. If this experience is typical, it may be possible to give, with the approval of the AEC, doses exceeding 200 mc with some increase in the risk of complications accepted when the clinical condition warrants it.

Restrictions on the millicuries retained

limit the effectiveness of the treatment in the very patients who are most suitable. No other solution to the increased radiation complications has as yet been found. Actually there seems to be little choice among millicurie administered, millicurie retained at 48 hours and rads to blood as a means of predicting radiation damage, and each was necessary to predict all of the complications shown in Table III.

The argument for large single doses of I^{131} in the treatment of thyroid cancer is based on evidence that radiation, either from isotope or external beam, may destroy the ability of the tumor to concentrate I^{131} without destroying its ability to grow.¹⁹ This retrospective review of patients treated was not considered to be a good way to evaluate such evidence, since patients with tumors losing their ability to function would not be treated or retreated. Notwithstanding, it appeared more reasonable to administer large doses to destroy not only function but the growth of functioning tumors. In addition, the clinical urgency for effective treatment was another factor justifying as large a dose as was relatively safe. Furthermore, in this series, doses of I^{131} smaller than 100 mc produced significantly fewer remissions than were obtained following the administration of larger doses.

At present, the reason why lung metastases are more, and lymph node lesions less, susceptible to radioiodine treatment is unknown. There is no doubt that the availability of chest roentgenograms facilitated follow-up study in the presence of lung lesions. The difference seems too large to be explained by this factor alone. A word of caution concerning the interpretation of survival figures is perhaps indicated. One should remember that the I^{131} treated patients had distant metastases and thus might have been expected to have a poorer prognosis than the total group (Table I), which included a large number of patients with local involvement only.

The results of therapy of thyroid cancer are highly dependent on the types of patients selected for treatment. The degree of

concentration of the I^{131} in the tumor surely affects the results. Furthermore, the retention required before the patient is considered suitable for treatment is variable from hospital to hospital, physician to physician and time to time. The clinical urgency and the possibility of other approaches to treatment also bear upon the decision to treat. Thus, among patients treated, results may vary. When an attempt is made to relate these results to all patients with thyroid cancer, all patients with metastatic thyroid cancer or all patients with metastatic, follicular thyroid cancer in lungs, difficulties arise. Although only the minority of all patients with thyroid cancer benefits from I^{131} treatment, with proper selection it should be possible to benefit about half of those treated. The sustained decrease in metastases in 27 per cent of the patients in this series confirms the value of treatment with radioiodine.

SUMMARY

1. In the 14 years since October, 1946, 59 patients were given 122 doses of I^{131} in the treatment of functioning, metastatic thyroid cancer. A method for prescribing the largest, relatively safe dose is presented.
2. The doses ranged in size from 6 to 600 mc and averaged 194 mc. The blood total radiation averaged 267 rads or 1.15 ± 0.06 rads per millicurie in 85 doses with adequate data.
3. When stimulation of tumor collection of I^{131} by antithyroid drugs was used before the tracer study, it was necessary to repeat the stimulation before the therapy.
4. Radiation side effects were frequent but were of a serious nature after only 11 per cent of the doses.
5. Bone marrow depression and radiation pneumonitis were each responsible for 2 treatment deaths.
6. Serious complications were related either to a blood total radiation exceeding 200 rads, the administration of more than 300 mc or the retention of more than 150 mc at 48 hours after the treatment.
7. Objective beneficial results occurred in 46 per cent of the patients treated and

were sustained in 27 per cent. No effect on survival was observed.

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LABORATORY PRODUCTION OF SHORT LIVED RADIOISOTOPES

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RECENT improvements in the design of fast neutron accelerators have placed the production of short lived radioisotopes within reach of the smallest laboratories. Isotopes such as sodium 24 with a half-life of 15 hours, magnesium 27 with a half-life of 9.5 minutes, aluminum 28 with a half-life of 2.3 minutes and many others can be produced by the bombardment of various elements by 14 million electron volt (mev.) neutrons from a small portable fast neutron generator. Typical of the nuclear reactions resulting from such a bombardment are:

- (1) $^{12}\text{Mg}^{24} + {}^1_0\text{n}^1 \rightarrow {}^{11}\text{Na}^{24} + {}^1_1\text{H}^1$
- (2) $^{13}\text{Al}^{27} + {}^1_0\text{n}^1 \rightarrow {}^{12}\text{Mg}^{27} + {}^1_1\text{H}^1$
- (3) $^{14}\text{Si}^{28} + {}^1_0\text{n}^1 \rightarrow {}^{13}\text{Al}^{28} + {}^1_1\text{H}^1$

APPARATUS

We have demonstrated this technique in the laboratory using a Picker-Dresser Type 2920 neutron generator as the neutron source. The Picker-Dresser neutron generator (Fig. 1) is an accelerator-type neutron source especially designed for research and educational purposes with a neutron output of up to 10^8 neutrons per second. The neutrons are substantially monoenergetic at 14 mev. The accelerator is small (diameter—4 inches, length—35 inches) and light (25 pounds) which makes it very portable. A scintillation counter consisting of a $2\frac{1}{4}$ by 5 inch sodium iodide crystal with a 6292 photomultiplier tube was used in conjunction with an Atomic Instrument Company Model 510 single channel pulse height analyzer and a Berkeley Model 2000 decade scaler to determine the half-life, energies and amount of the isotope produced. The only other equipment needed was the usual chemical apparatus necessary to perform the simple chemical separations involved.

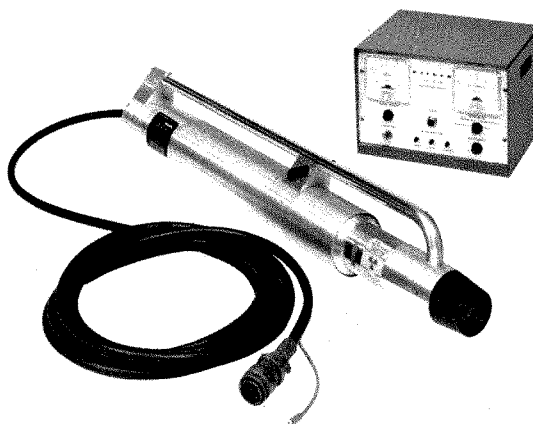


FIG. 1. The Picker-Dresser neutron generator.

PROCEDURE

Metallic magnesium powder weighing 8.75 gm. was placed in a plastic container and wrapped around the neutron accelerator directly over the source target. The accelerator was turned on and adjusted to an output of 10^8 neutrons per second and left at this output for a period of $16\frac{3}{4}$ hours. During this period of time the 14 mev. neutrons were continuously bombarding the magnesium and producing protons and sodium 24. At the end of the activation period, the accelerator was turned off and the activated sample removed and transferred to a small vial. Care was taken in the handling of the newly produced isotope to avoid any hazardous exposure. The hazard with this small sample is, of course, primarily internal. The amount of activity produced was then determined by simply comparing the counting rate produced by the sample with that produced by a small thorium 228 source of known strength. This could be done by direct comparison due to the fact that both sodium 24 and thorium 228 produce photo peaks (100 per cent) at approximately 2.7 mev.

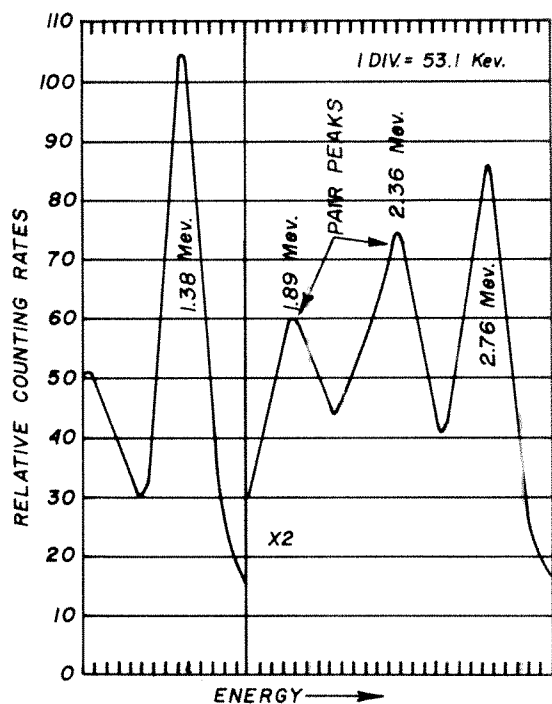


FIG. 2. Gamma-ray spectrum of produced radioisotope.

The sample was then transferred to a beaker containing 100 cc. of concentrated hydrochloric acid. This, of course, by the reaction $\text{Mg} + 2\text{HCl} \rightarrow \text{MgCl}_2 + \text{H}_2 \uparrow$ brought the magnesium into the chloride form. Enough sodium hydroxide was added to the solution to precipitate all of the magnesium in the form of magnesium hydroxide:



The magnesium hydroxide was filtered off leaving a sodium chloride solution with the radioisotope sodium 24.

The scintillation counter was immersed in the NaCl solution and an integral bias curve was made to verify the 1.368 and 2.754 mev. photo peaks as well as to obtain an initial count to verify the half-life (Fig. 2). Two additional measurements were made after intervals of approximately 18 and 24 hours. These points were plotted on semilog paper and the half-life determined (Fig. 3). Upon completion of the

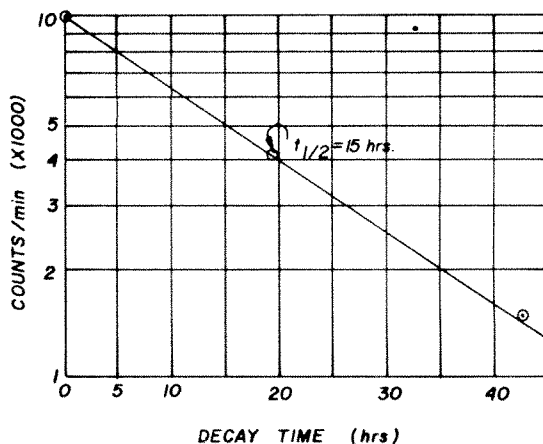


FIG. 3. Half-life curve for produced radioisotope.

experiment, the magnesium hydroxide precipitate was checked for any activity.

RESULTS

The half-life determination showed that we had produced a radioisotope with a half-life of 15 hours (Fig. 3). The integral bias curve clearly identified the sodium 24 photo peaks (Fig. 2). The comparison with the known 10 μC thorium source showed that we had produced 1.1 μC of sodium 24. The Geiger-Müller counter examination of the filtered magnesium hydroxide precipitate showed no activity and, therefore, all the sodium 24 produced from the activation of the magnesium was in the sodium chloride solution.

CONCLUSIONS

The advantages of this technique are obvious. Not only does it make tracer amounts of short lived isotopes immediately available without the usual two to three week wait for delivery from isotope suppliers, but it provides a means of obtaining many isotopes which are not available commercially due to their short half-lives.

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AN INSTRUMENTED PHANTOM SYSTEM FOR ANALOG COMPUTATION OF TREATMENT PLANS

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IN GENERAL, the clinical practice of radiotherapy is based on depth dose data and isodose curves derived from geometrically simplified, homogeneous phantoms employing water or pressdwood as a tissue-equivalent medium. These data are used to compute dose distributions within patients whose contours are very different from those of the phantom, and who are complex admixtures of bone, soft tissues, fluids, and air. The treatment is administered with apparatus which may deviate widely from the research apparatus with which phantom measurements were made.

It is not surprising, therefore, that many studies^{10,12} show a variety of substantial errors intervening between depth dose data and their final utilization within the patient. There are many sources of error, including uncertainties in the basic data, errors in machine calibration and output, errors in computation, errors due to inadequate correction for bone, air, and fat, errors in positioning, etc. A major portion of these errors is associated with this relationship between the phantom data and the actual treatment.

A primary source of error would be bypassed if a structurally differentiated phantom were used. With such a phantom, dose distributions could be derived routinely for specific treatment problems, using the actual treatment apparatus. Thus, if the correspondence between phantom and patient were close enough, the often complex treatment computations necessary with conventional phantoms would be virtually eliminated. The dosimetry system of the

phantom would integrate all entrant radiation from whatever sources, so that the most complex treatments, involving multiple fields, rotational therapy, or supplementary fields, would be measured as readily as the simplest fixed-beam treatment.

The success of such a system depends upon closely matching phantoms with patients, upon accurate dosimetry techniques, and upon the solutions to many practical problems related to clinical use. This paper is a first report on studies being carried on to establish a system, which we call "analog dosimetry," as a working tool for the radiotherapist.

BACKGROUND FOR PHANTOM DEVELOPMENT

A number of basic criteria was established from the outset for the design of the first phantoms to represent the human body closely and thus to serve as substitute or analog patients.

- a. They must include natural bone, soft-tissue and lung-tissue equivalent materials. (Fat could be considered at a later time.)
- b. They must have a composition such that the absorbed dose would correspond closely to that in the human body over the entire range of roentgen ray, gamma ray, and electron energies in therapeutic use.
- c. They must be compatible with the systems of dosimetry in use in radiotherapy departments.
- d. They must be rugged and serviceable and capable of placement upon treatment tables in a variety of standard positions.
- e. They must be constructed by produc-

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tion processes for accurate duplication.

No existing phantoms approximate these requirements. Water phantoms with movable probes are not practical for application to analog dosimetry in regular hospital use, nor rugged enough for this service. The most elaborate water phantom, available commercially under the trade name REMAB,¹¹ is designed for use with pre-selected and limited dosimetry points intended for health-physics studies. Its dosimetry system is not adequate for refined therapeutic measurements.

Laminated presswood phantoms present an excellent approach to the problem of obtaining ready access for instrumentation everywhere within the interior, but the installation of a skeleton does not appear feasible from a production standpoint (although it was accomplished in a research phantom by Laughlin *et al.*⁸). Moreover, since presswood is manufactured primarily as a building material, its absorption characteristics are subject to considerable variation.⁶

In the course of our work, a decision was made to develop a solid phantom consisting of a tough, thermosetting plastic with the correct radiation absorption characteristics, which could be cast in the desired shape. The casting would be made around a skeleton, lung equivalents, and other structures. (Some of the materials and techniques needed for this process had already been developed for the Picker-Alderson pelvic phantom.¹) The phantom could then be sawed into transverse sections, and the sawed faces coated to achieve flat, finished surfaces.

Two prototypes of such a phantom were completed successfully by this procedure in October, 1960. They have been in use at the Argonne Cancer Research Hospital, Chicago, Illinois, and at the Montefiore Hospital, Bronx, New York, for research in phantom dosimetry.

Thereafter, work was begun on the standardization and control of materials and processes. Methods of equipping the phantom with a dosimetry system for use on a

routine basis were investigated. This work led to the completion in March, 1961, of the first phantom to be made entirely by production techniques (Fig. 1).

THE AVERAGE MAN PHANTOM

Size. In the development of the above phantom, a suitable size had to be decided upon. The proportions chosen were based on a military anthropometric survey,⁴ modified slightly to conform with the results of a civilian survey.⁵ If the phantom

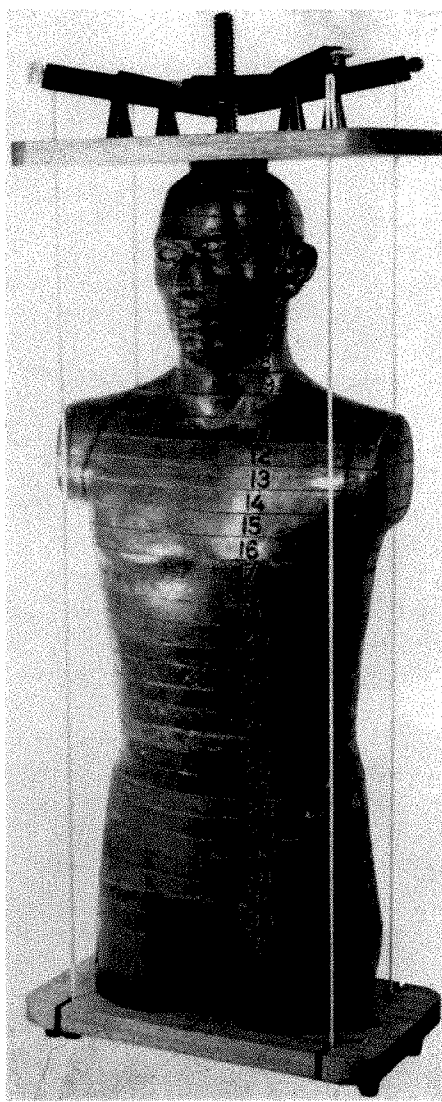


FIG. 1. Complete phantom in clamping device. The sections are individually numbered.

were a complete body (Fig. 1), it would be 5 ft. 8 in. tall and weigh 162 lbs. Although we term this an "average man," such a designation is of little clinical significance, since the problem is one of correspondence with an enormously variable population. Hence, size chosen in this instance is somewhat arbitrary. Any size chosen for an average man would change only slightly the magnitude of the problem of matching phantoms to a broad range of patients.

Materials. The phantom contains a natural human skeleton of appropriate size, adjusted within the mold to normal relationships with body contours. Molded in a dried condition, it is later impregnated with soft-tissue equivalent material to replace the lost constituents.

The soft tissues are molded of an extremely tough plastic based on a synthetic isocyanate rubber. The material is stable with respect to aging, temperature, humidity, and other environmental conditions; it is resistant to abrasion, laceration, and impact, and it does not deteriorate under radiation (it has withstood 1.1 million r without any discernible changes).

It is processed chemically and physically to achieve a specific gravity of 0.985 and an effective atomic number of 7.30. These values, based on the ICRP Standard Man,¹³ represent a composite of muscle, nominal body fat, fluids, etc. In production, they are kept constant with an accuracy of ± 1.25 per cent for specific gravity and ± 0.5 per cent for effective atomic number. Thus, the material is sensibly tissue-equivalent over the entire range of therapeutic energies in common use today.

Figure 2 shows a partially molded phantom with lungs, trachea, and skeleton. The lungs are molded of an air-expanded version of the soft-tissue material, having the same effective atomic number but a specific gravity of only 0.3. The lung material is a mechanical foam of small and uniform cell size; it is rigid and dimensionally stable. The lungs are sculptured to a neutral respiratory volume; the left lung is smaller to allow for the heart. The tra-

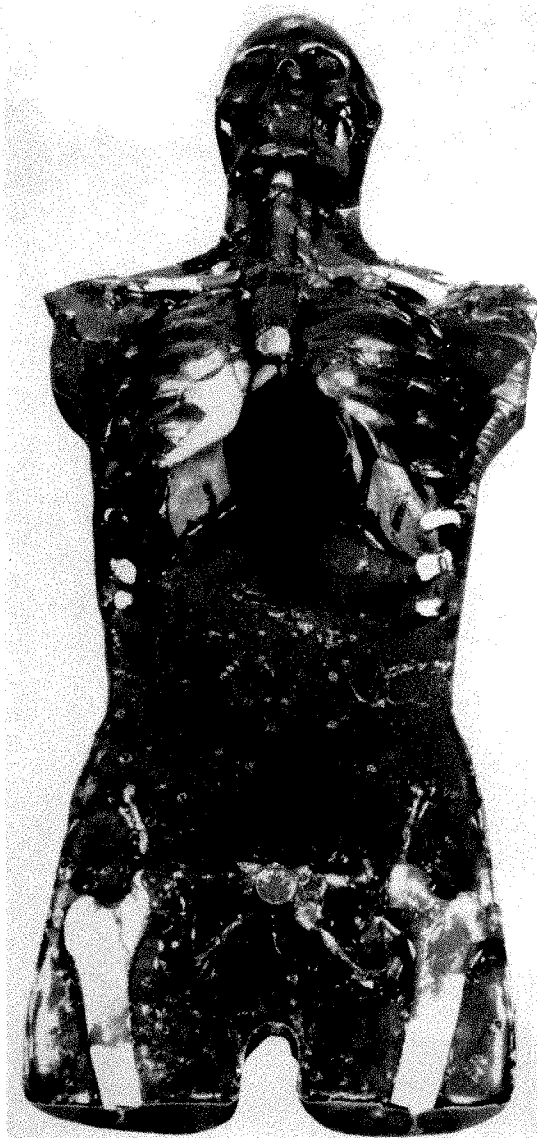


FIG. 2. Partially completed phantom during manufacture. The skeleton and lung inserts are visible.

chea shown in the photograph is a mold insert, representing normal air content; this insert is removed after molding, leaving air spaces.

Sections. Figure 3 illustrates the slicing of the phantom. The sections are sawed to a thickness of approximately 0.965 inch; they are then impregnated to restore the soft-tissue content of the bone segments and coated on each side to build up a protective surface over the bare ends. These

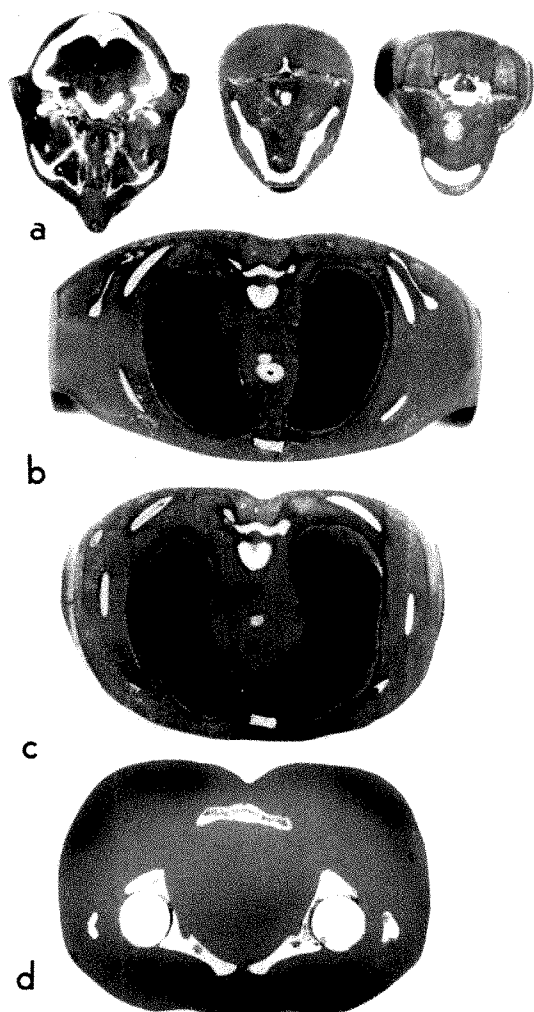


FIG. 3. Sections of sliced phantom showing (a) teeth and skull; (b) and (c) lung equivalents and bone in the thorax; and (d) skeleton in the pelvis.

coatings are machined and polished to give a finished thickness of 0.984 ± 0.005 inch or 2.5 cm. The soft-tissue overlay on bones is a discrepancy of minor significance. The coated material is a slightly heavier (specific gravity 1.05) transparent modification of the tissue-equivalent material, and forms an integral bond with the underlying section.

There are some apparent discrepancies between bones visible on the right and left sides. These are slight variations in bone level, attributable to the difficulty in attaining machine precision in the placement

of variable skeletons within a 3-dimensional mold. We believe that a transected cadaver also would show slight skewing and asymmetries.

Assembly. Figure 4 shows a random portion of the phantom assembled in a clamping device. Any group of consecutive sections may be thus assembled, including the entire phantom. There is, however, little reason for assembling the complete phantom in radiotherapy (other than for exhibition purposes); in general, the sections containing the tumor region would be used, plus buffer sections at both ends to provide equivalent scattered radiation.

The base plates are made of thick, warp-resistant mahogany. The few metal parts used on the bases (outside the radiation beam) are needed because the clamping forces will normally be of the order of 200 pounds. The nylon center wheel has a square-form thread for smooth action and strength; the mechanical advantage of the system is such that full clamping pressure is attained with nominal torque on the wheel. The design produces equal pressures at all cords; if one cord interferes with a

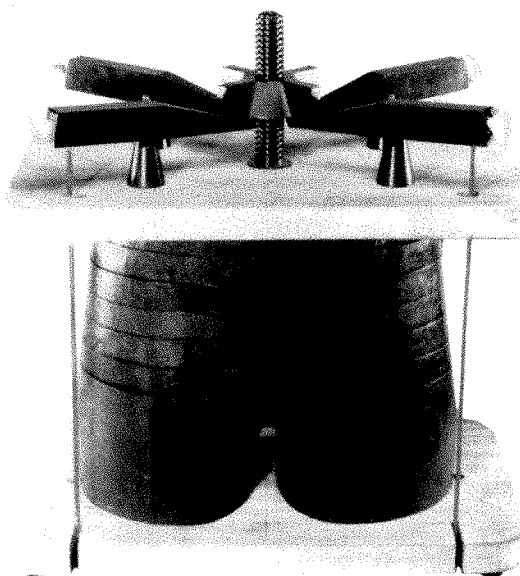


FIG. 4. Sections of phantom held by clamping device. Nylon cords are used in tension to hold sections rigid during irradiation.

roentgen-ray cone, it may be removed and 3-cord operation used without essential impairment of stability.

The sections fit together by two small ball-and-socket registrations formed by pressing in molded cellulose acetate butyrate rods of $\frac{1}{4}$ inch diameter; there are three different spacings for sections of various sizes. Multiple registration points are available on each base plate, with interchangeable nylon fittings, so that any section may be accommodated next to any base plate. This is exclusive, of course, of the pelvic-thigh section (not sliced) which fits only to the bottom plate, and of the top of the head which is registered by a nylon ring to the top plate only.

In assembling any desired grouping of sections, the thumb screws at the ends of the levers are loosened, the nylon cords are drawn snug, and they are then relocked by the thumb screws. Spinning the central wheel establishes an accurately aligned assembly. For repetitive use, the cords may be unhooked and removed from slots in the bottom plate so that cord length and thumb-screw adjustments are not changed.

A series of radiographs of various segments of the phantom located within the clamping device is shown in Figure 5, *A*, *B* and *C*. Standard diagnostic settings were used in the making of these radiographs.

DOSIMETRY SYSTEMS

A body section passing through the tumor is a common starting point in treatment planning. The problems associated with the computation of dose distributions in planes above and below the tumor are too complex for routine solution. Analog dosimetry, on the other hand, does not present such problems. Direct measurements can be made in two or more sections of the phantom, located at various levels of the tumor region.

A knowledge of dose distributions in several planes within the tumor volume is desirable to insure that the treatment plan to be used provides a minimum tumor lethal dose without "hot" or "cold" spots.

Furthermore, the maximum dose should be confined well within the boundaries of the tumor, so that the dose in normal tissues is minimal. Hematopoietic tissues, the spinal cord, the rectum, scar tissue, and other sensitive tissues should receive minimal doses, and the integral body dose kept as small as possible.

These considerations indicate the need for many points of dose measurement and a high degree of flexibility in their location. To achieve this, basic instrumentation plans were studied against these criteria:

a. Dosimeters should have a small volume to avoid field distortion and in order to give as close to point measurements of dose as possible.

b. Dosimeters should be capable of calibration or simple conversion to absorbed dose. Such calibrations would be to the muscle-equivalent tissues which approximate the composition of most tumors.

c. Integrating dosimeters would be required for rapid and routine use (particularly in multiple field and rotational therapy); they must have a high dose capacity to avoid brief samplings of distributions which might lead to substantial timing errors.

d. The dosimeters should be as nearly energy independent as possible and be independent of dose rate and direction.

e. They should be reliable, rugged, stable, precise and capable of routine use by hospital personnel.

Two general types of dosimetry systems have been given consideration and are now being subjected to intensive study: intracavitary type ionization chambers and film. Neither system is optimal in all respects, but both appear to be practicable. In addition, new approaches to dosimetry are now under study, including glass dosimeters, solid state detectors, etc.

Ion Chambers. Several types of intracavitary ion chambers have been used successfully in clinical practice and in phantom work for obtaining isodose curves. One such study of particular interest has been reported by Dahl and Vikterlöf.²

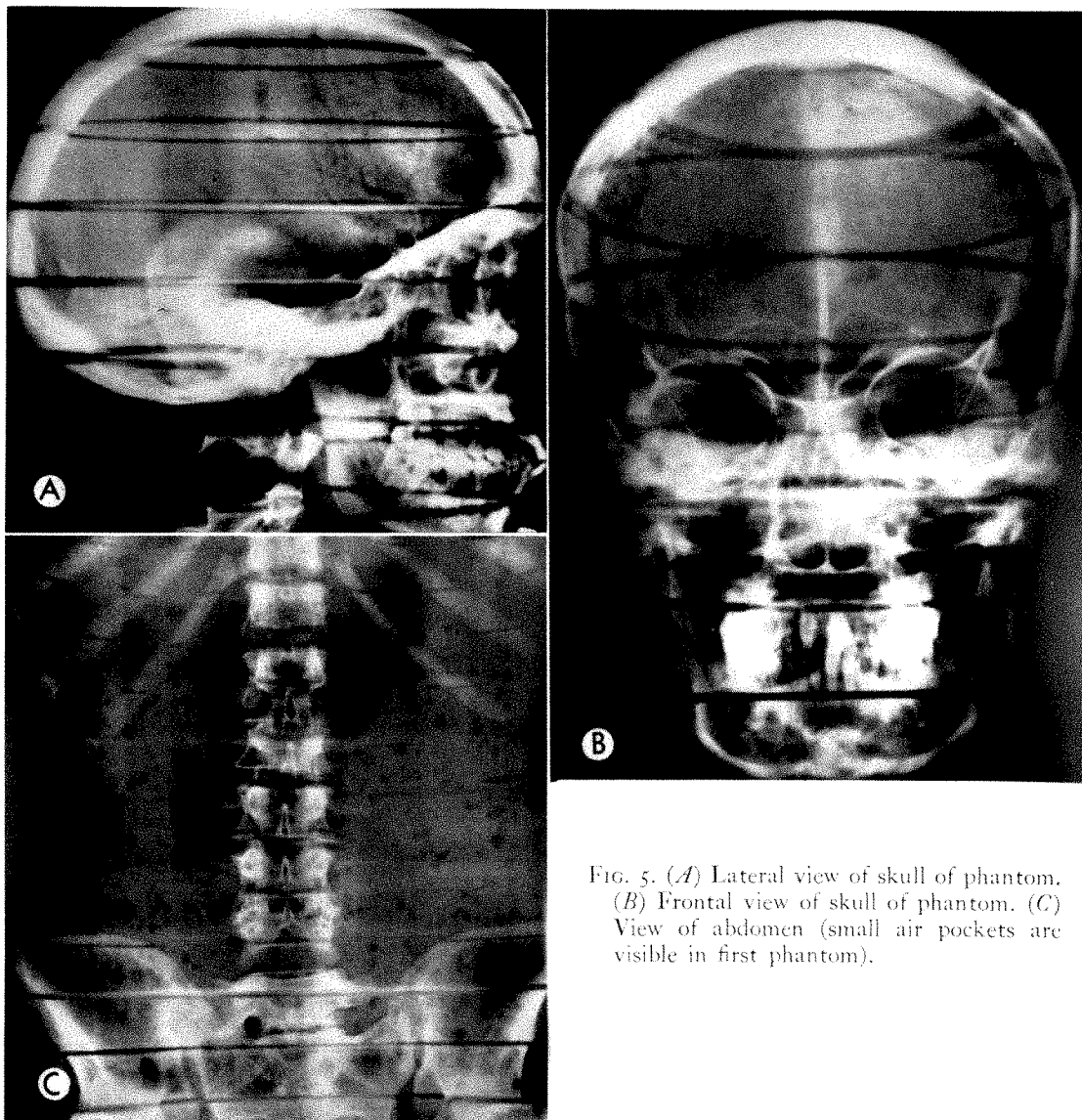


FIG. 5. (A) Lateral view of skull of phantom. (B) Frontal view of skull of phantom. (C) View of abdomen (small air pockets are visible in first phantom).

Figure 6 shows a section of our phantom with ion-chamber insertion holes drilled through in a rectilinear grid array with a 3 cm. spacing. This spacing was selected reluctantly after consideration of the number of holes which would be required for finer grids. In body regions of mixed composition where isodose curves will be irregular and often very closely spaced, 3 cm. intervals might fail to disclose abnormalities in the distribution.

Two general approaches are being made to this problem, which will occur frequently

in clinical practice. The simplest solution is to drill an additional hole or holes whenever such a situation is met, thus obtaining closer spacings on an *ad hoc* basis. It has been established that simple drilling of a section, without reaming or other precision methods, produces a hole of good surface finish with reasonable diametral tolerance. A more complex solution is to supplement ion chamber dosimetry with film dosimetry in such cases. Although the energy response of film is nonlinear at low energies (see below), it can be used in this manner, since

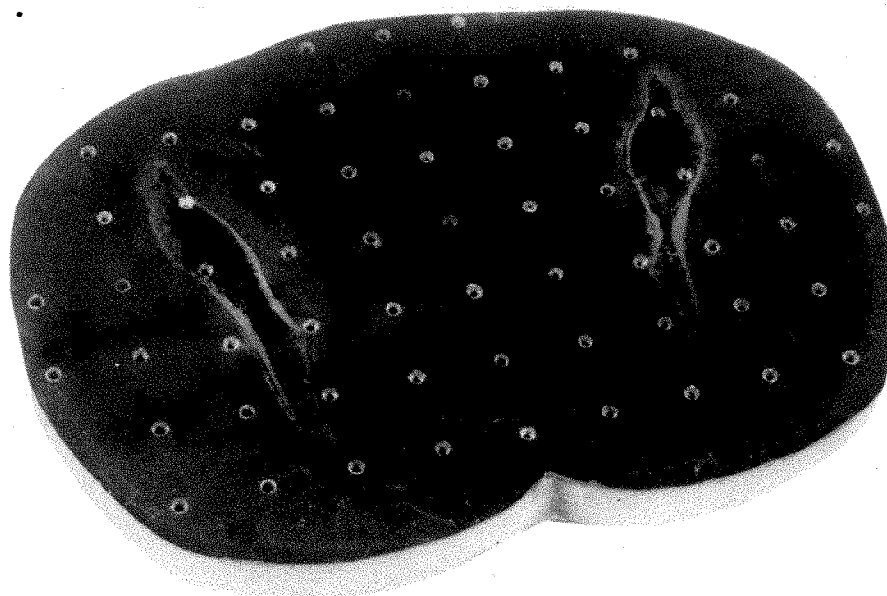


FIG. 6. Section of phantom showing holes for ion chambers.

the ion chambers will yield calibration points.

It may be noted that the use of multiple chambers also provides a continual check on their accuracies. One study¹² has reported occasional chamber malfunction without apparent cause; where the chamber is a prime calibration standard in a radiotherapy department, the consequences may be serious. If a chamber is one of 25, 50, or more in a grid, its malfunction will become as apparent as an incorrect datum point on a curve.

The system now being standardized is based upon ion chambers 5 mm. in diameter and 20 mm. long. Accuracy standards of 5 per cent have been established as the minimum permissible. Studies are in process to narrow this range by dividing chambers into subgroups according to calibration factors.

Commercially available charger-readout units are being evaluated. Stable and reliable instruments are available to permit these processes to be carried out rapidly and accurately. Figure 7 shows a data chart intended for use in conjunction with the phantom for both ion chamber and film

dosimetry. In clinical use, all holes not occupied by chambers will be filled with injection-molded Mix D plugs. Sections containing chambers will be brought to the readout unit for dose measurement, and the value noted in the appropriate datum box on the chart; thus, numbering or other complex handling of chambers is avoided.

Essentially, ion chamber dosimetry is completely practicable for routine use. Initial purchase costs are substantial, but the chambers have indefinite service lives. If checked routinely, they provide a basis for consistently accurate dose determinations everywhere within the phantom.

Film Dosimetry. Film measurement of dose distributions at the interfaces between phantom sections is a quite simple procedure in principle. Examples of film dosimetry are described in the literature.^{3,7,9} For use in the phantom, film sheets are inserted between and brought into intimate contact with the sections by applying uniform clamping pressure. After irradiation, the films are developed and readings are made on a photodensitometer at any desired number of points.

The data chart of Figure 7 is printed on

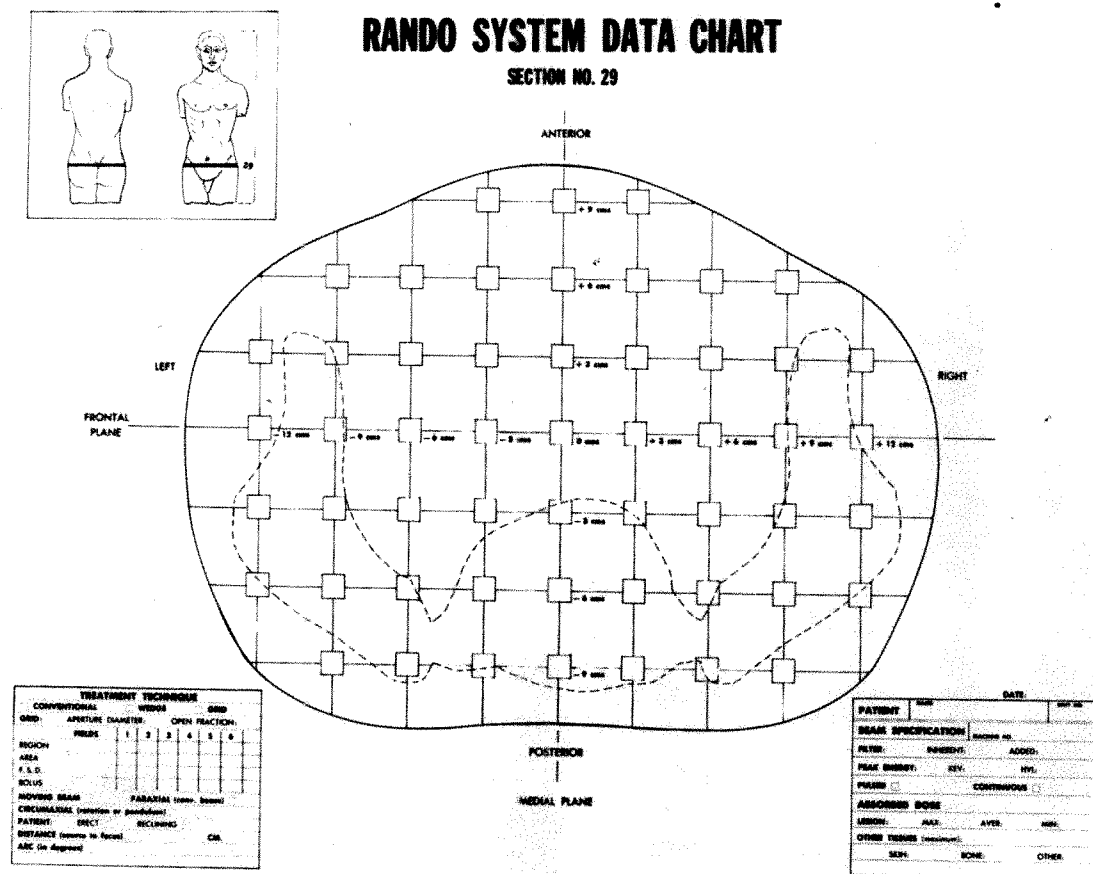


Fig. 7. Chart for recording physical data of irradiation from which isodose distributions can be constructed.

transparent vellum and is used as follows for film dosimetry: After the tumor outlines are drawn in, any points at which dose values are desired may be marked on the chart in addition to those in the data boxes on the grids. The film may then be superimposed on the chart over an illuminated box and these points encircled in grease pencil. Thereafter, dosages converted from photodensitometer readings at these points are recorded on the chart.

There are, however, many complicating factors in film use. Since virtually all commercial film contains silver bromide, which deviates widely from soft-tissue equivalence, film response is nonlinear at ordinary therapeutic roentgen-ray energies (below about 0.3 mev.). Calibrations at lower energies are of limited value, since secondary or degraded radiation presents a con-

tinually variable energy range. Present research confirms the accuracy of high dose capacity film at cobalt 60 energies. Results of this work are to be published in the near future. Work is continuing on cesium and radium sources.

Film dosimetry has the advantage of providing as many data points as desired. In contrast to ion chambers, initial costs are considerably lower, but film constitutes a continuing cost burden to a radiotherapy department. In those energy ranges where its use is indicated, accuracy can be held to within about 5 per cent by control of developing processes with respect to time, temperature, agitation, and age of the solutions.

Present research tends toward the view that darkroom loading of film is needed. The erratic results obtained with film

packaged in individual paper cassettes are due primarily, it is thought, to the effects of entrapped air. A simple folder of black paper, pressed smoothly to expel air, appears to give uniformly accurate results.

In practical use, the sections to be interleaved with film will be taken in to the darkroom for installation. Film sheets will be pre-punched to slip over the section registration bosses (thus establishing the geometry of the dosimetry system) and placed between sections. Taping of edges to exclude visible light may not be necessary because of the slowness of the film and the good fit of the sections.

Calibration problems are now being studied also. It appears at this time that density below the surface for cobalt 60 energies may be predetermined by ion-chamber measurements and utilized directly for calibration, rather than requiring companion films to be exposed for this purpose. This is a preliminary finding, and one not to be accepted until experimental work has been completed.

COORDINATE SYSTEMS

The radiation analog dosimetry system (RANDO) is based upon a Cartesian coordinate system; the Z-axis is the longitudinal axis of the body; the X-axis lies in the principal coronal plane; the Y-axis lies in the median plane of the body. Sections are numbered from 0 to 35, interfaces from 1 to 35, with each interface bearing the number of the lower of the matching sections. Looking down at an interface, the X-Y plane is seen. Figure 6 shows this coordinate system. The data boxes at the intersections of the ion chamber grid are numbered from the origin on the Z-axis, positive being anterior or right side, negative being posterior or left side.

The transparency of the data sheets allows ready transfer of data points. This also serves to facilitate reproduction if treatment atlases of data sheets are compiled by cooperating institutions.

The coordinate systems are carried into the orientation of the phantom on the

treatment table. The clamping device and plates and registrations are so proportioned that the Z-axis is always parallel to the table, whether the phantom is prone, supine, or on its side, and for any grouping of sections. This is intended to assist in the alignment procedure.

PATIENT ANALOGY

Analog dosimetry attains maximum accuracy with maximum correspondence between phantom analog and patient. The enormously complex structure of the human body is not amenable to minute and detailed correspondence. However, extreme accuracy is beyond the limits required in clinical practice, since neither the tumor lethal dose for a given case nor the tumor location and size are known with such precision.

In practice, some simplification is necessary and permissible, as used in the case of the bone, muscle, lung, and air space content of the Average Man. The exact extent of the effect of these simplifications on treatment accuracy is still to be determined in detail. However, even with some divergence between phantom and patient in bone size and placement, far higher accuracy is achieved than by the application of theoretic correction factors.

Among the factors still to be investigated are the effect of the respiratory cycle on thoracic dose and the accuracy limits of a phantom in a static respiratory condition; gastrointestinal content; the effects of fascia (with much higher specific gravity than muscle tissue). Many other variables of the human body must be studied and error limits assigned. We must still deal with variations in size, body build, contour and fat content. A continuing program of research development is planned to elaborate the system in these respects.

At this time, three techniques are being studied:

a. *Correspondence by Phantom or Patient Build-up.*

An emaciated patient may be brought into correspondence by adding a muscle-

tissue-equivalent deposit, in gel or wrapping form. A fat or edematous patient may be matched by adding fat-equivalent or muscle-equivalent build-ups to the phantom.

b. *Re-contouring.*

A female phantom is currently under development; the system includes a transparent, rigid brassiere in regularly graded sizes. The brassiere cup will bring the patient's breast into accurate shape correspondence with the phantom; interchangeability of phantom breast sections will establish size correspondence. A very close relationship will thus be established. Similar techniques will be developed for other parts of the body.

c. *Multiple Sizing.*

There are few anthropometric studies of a population of the most common age group of cancer patients. Such a study must be undertaken to establish a phantom size range on rational grounds. Reducing the number of phantom sizes to a minimum is an economic imperative; having an adequate number is a therapeutic necessity.

A program is being initiated to explore numerous other possibilities for expanding the range of the system.

CLINICAL APPLICATIONS

The system of analog dosimetry presented here is oriented toward practical use in the radiotherapy departments of both large and small institutions. Its contributions will be at a minimum in the treatment of responsive skin cancers, at a maximum in the many intricate treatment problems which confront the radiotherapist.

For example, there are few depth-dose charts or isodose curves which can be applied with reasonable assurance for tangential fields in breast carcinoma. The difficulties are compounded by the need to provide idealized bolus set-ups. By establishing a highly accurate correspondence between phantom and patient breasts, utilizing the contouring brassiere, dose distributions may be established with far

greater precision and certainty than possible hitherto. Such distributions will relate not only to the breast area, but also to the axilla, chest wall, adjacent lungs, and internal mammary fields.

Another example which illustrates the need for an inhomogeneous human substitute is the treatment of carcinoma of the lung. Much work has been done in the past on correction factors to allow for diminished absorption and scatter in lung. Their use leads to considerable error in attempting to estimate dose distributions within the tumor and surrounding tissue, particularly when oblique or tangential fields are utilized. A much more precise dose distribution is attained by placing dosimeters within an accurate, patient-adjusted phantom, and actually measuring the dose from the various fields to be used. The final results, including beam alignment, can readily be transferred to the patient.

A major consequence of analog dosimetry may be the increase in sophistication and complexity of treatment plans which can be carried out with accurate knowledge of dose distributions. Frequently, optimal dose distributions may be obtained by multiple fields, precisely controlled rotations, radium or roentgen-ray supplements, and other techniques. With the analog dosimetry system, the most complicated treatment plan is evaluated as simply as any other, avoiding the complexities of calculating the dose distributions.

SUMMARY

Realistic phantoms, molded of accurate tissue-equivalent materials, and containing natural skeletons, lungs, and other structures, are integrated with ion chamber and film dosimetry systems. The objective is to reproduce patients in sufficient detail to test and correct treatment plans by analog methods, thereafter transferring such treatments to the patient. By continued research and development into patient-phantom correspondence, a considerable contribution to improved accuracy in radiotherapy is anticipated. Treatment computation

may be bypassed by analog dosimetry, and the possibility of achieving extensive and practical treatment atlases is considered.

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THE AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE

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Forty-fourth Annual Meeting: Waldorf-Astoria Hotel, New York, N. Y., April 2-4, 1962.

* *Ex officio.*

EDITORIAL

THE FORTY-FOURTH ANNUAL MEETING OF THE AMERICAN RADIUM SOCIETY

THE Forty-fourth Annual Meeting of the American Radium Society will be held at the Waldorf Astoria Hotel in New York City, April 2-4, 1962. A cordial invitation is extended to all members of the Society and also to other physicians and allied scientists who are particularly interested in problems related to the control of malignant disease. One of the objectives of the Society is to provide a common meeting ground for those individuals who have a major interest in cancer.

On the first day of the meeting there will be a symposium on supervoltage therapy, with J. W. J. Carpender, M.D. as moderator, which will provide a discussion in depth of the synchrotron, the linear accelerator, the betatron, cobalt 60 and two-million volt x-ray. A distinguished guest participating in this symposium will be Professor Sir Brian W. Windeyer of London, England. In addition to taking part in the symposium Sir Brian will address the Society as guest lecturer. On the first day's program there will also be several papers related to the use of supervoltage modalities in the treatment of cancer of the breast, bladder, and nasopharynx. Another highlight will be a discussion of clinical trials in the next decade by J. R. Heller, M.D., President of Memorial Sloan-Kettering Cancer Center. Still another presentation of considerable interest will be a symposium on the management of solid tumors of childhood with Harold W. Dargeon, M.D. as moderator. Paul C. Aebersold, Ph.D. will report on recent developments in isotope production and source fabrication and John S. Laughlin, Ph.D. will present a comprehensive implant dosimetry system.

On the second day of the meeting R. Lee Clark, M.D., Director of the M. D. Anderson Hospital and Tumor Institute, will discuss the clinical significance of recent progress in cancer research. An up-to-date report on clinical cancer chemotherapy will be given by Robert D. Sullivan, M.D. Roberts Rugh, Ph.D. will give a further report on his fascinating study of low dose x-ray effect on the mammalian embryo and fetus. William S. MacComb, M.D. will moderate a panel on carcinoma of the larynx. At 11:15 A.M. on April 3 the Jane-way Lecture will be given by Virginia Kneeland Frantz, M.D. on "Privileges and Challenges in the Study and Treatment of Thyroid Cancer." During the afternoon of April 3 George E. Moore, M.D., Director of the Roswell Park Memorial Institute, will discuss the importance to the radiologist of recent advances in cytology. Following this there will be a symposium on the modifying effect of chemotherapeutic agents on radiation response with Justin J. Stein, M.D. as moderator. Later in the afternoon Robert C. Hickey, M.D. will report on palliation attempts in human breast cancer by pituitary irradiation with focused ultrasound. Other excellent papers will be found on the program which is printed in detail elsewhere in this issue of the JOURNAL.

On the last day of the meeting Gould A. Andrews, M.D. of the Oak Ridge Institute of Nuclear Studies will report on experience with whole body irradiation. There will be two papers concerned with malignant tumors of the vagina and a discussion of the management of adenocarcinoma of the cervix. A report on fifty cases of chordoma with an evaluation of their man-

agement will be presented. Another symposium of current interest will be on the subject of preoperative irradiation with Calvin T. Klopp, M.D. as moderator. Once again let me urge you to look over the complete program carefully. All participants are highly qualified and we look forward to an outstanding and memorable meeting of the American Radium Society.

In addition to attending the Scientific Program just described the Forty-fourth Annual Meeting will be an occasion for renewal of friendships and for pleasurable social activities. A special invitation is extended to the wives of members and guests and we hope that you will all come. There will be a guided tour and luncheon at the United Nations for the ladies on Monday, April 2. On Tuesday evening following a reception given by the Radium Chemical Company the annual banquet and dinner dance will be held in the Sert Room at the

Waldorf-Astoria Hotel. The Arrangements Committee has plans for entertainment at the banquet and for other social activities which will be of interest to all.

Advance registration is encouraged. Members of the American Radium Society have already received registration forms. Please mail them in promptly if you have not already done so. Non-members interested in attending the meeting of the American Radium Society are advised to write to Lemuel M. Bowden, M.D., Chairman of the Arrangements Committee, for further particulars. Dr. Bowden's address is 177 East 79th Street, New York 21, New York.

ROBERT L. BROWN, M.D., *President*
American Radium Society

Robert Winship Clinic
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While the Subcommittee does not anticipate revision of Handbook 76 in the immediate future, a number of questions of interpretation of that handbook have arisen and the Subcommittee expects to deal with these problems as its first order of business.

Reorganization of Subcommittee 7 on Monitoring Methods and Instruments following the retirement from NCRP activities of the former Chairman, H. L. Andrews, is presently underway. A new Chairman, Arthur R. Keene, has been selected, and the following have been named members of the Subcommittee:

A. R. Keene, Chairman	R. T. Mooney
J. S. Handloser	J. Ovadia
M. Ehrlich	W. C. Roesch
J. S. Krohmer	E. W. Webster

It is planned that the Subcommittee will write a new handbook to replace Handbook 51 (NCRP Report No. 10), "Radiological Monitoring Methods and Instruments" which was published in 1952 and hence is somewhat out of date.

It has recently been brought to the at-

tention of the NCRP that the increasing use of radiation-producing equipment in high school and college classrooms presents a radiation protection problem which has received very little attention up to the present. The Executive Committee of the NCRP has now authorized the establishment of a subcommittee to review this problem with the intent to formulate recommendations on this area. Professor F. Shore of Queens College has agreed to chair the Subcommittee. The activities of this Subcommittee are to be coordinated with the activities of the Committee on Apparatus for Educational Institutions of the American Association of Physics Teachers which is very much interested in the formulation of recommendations applicable to this area and in the dissemination of such recommendations to the teaching profession. The United States Public Health Service has tentatively agreed to carry out such field studies as may be necessary to obtain some of the operational information needed by the Subcommittee.



NEWS ITEMS

THE AMERICAN BOARD OF RADIOLOGY

The American Board of Radiology makes the following announcement:

The Spring 1962 examination will be held at the Terrace Hilton Hotel, Cincinnati, Ohio, June 18-22, inclusive, 1962. The deadline for filing applications was January 1, 1962. A special examination in Nuclear Medicine for Diplomates in Radiology or Therapeutic Radiology and an examination in Radiological Physics will be held if there are sufficient applications.

The Fall 1962 examination will be held at the Pioneer Hotel, Tucson, Arizona, the first week in December; the deadline for filing applications is July 1, 1962. Please note that at this session Nuclear Medicine will become a mandatory part of the examination. All candidates, excluding re-examinees, who are applying for examination in Radiology or Therapeutic Radiology for the December 1962 session or thereafter must submit a Nuclear Medicine application in addition to their basic application. This applies even to those applicants whose basic applications are on file but who will not yet have appeared for examination.

THE 1961 W. EDWARD CHAMBERLAIN LECTURE

The 1961 Lecture correlating physiology and radiology, honoring W. Edward Chamberlain, M.D., Emeritus Professor of Radiology, Temple University School of Medicine, was given on November 22, 1961, by Björn Nordenström, M.D., Director, Roentgen Department, Thorax Clinic, Karolinska Hospital, Stockholm, Sweden. The subject was: Methods of Altering Circulatory Dynamics to Improve Roentgen Examination.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS

The Association of University Radiologists has elected the following officers for 1961-1962: President, Robert D. Moseley,

Jr., M.D., Chicago, Illinois; President-Elect, Melvin M. Figley, M.D., Seattle, Washington; and Secretary-Treasurer, Herbert M. Stauffer, M.D., Philadelphia, Pennsylvania.

COLLEGIUM ORBIS RADIOLOGIAE DOCENTIUM

The conference of university professors of medical radiology which was arranged by Professors Schinz and Cocchi of the University of Zürich under the provisional title of a "World Association of University Professors of Medical Radiology," and convened in Zürich October 13-15, inclusive, 1961, determined to formally establish the "Collegium Orbis Radiologiae Docentium" (C.O.R.D.), with the following Executive Committee:

President:	Professor Hans R. Schinz (Switzerland);
Vice-President:	Professor Luigi Turano (Italy);
Secretary:	Professor U. Cocchi (Switzerland);
Treasurer:	Professor Guy R. Ledoux-Lebard (France);
Members at Large:	Professor Josef Becker (Germany); Professor Carleton B. Peirce (Canada); and Professor B. G. Ziedses des Plantes (The Netherlands).

Various problems were discussed. Arising from the deliberations of the conference, the following conclusions are currently announced for the information of those concerned:

It was the consensus of the conference concerning:

A. Radiation Protection in Hospitals:

1. As the accomplishment of radiation protection in hospitals requires and presupposes a comprehensive special knowledge of radio-diagnosis and therapy, as well as radiobiology,

radiation physics and cognate applied science, its responsible direction must be in the hands of the senior physician in medical radiology of the hospital.

2. The senior medical radiologist must see that the rules and regulations governing protection against radiation, both as laid down in law and as recognized internationally are observed for the protection of patients and staff.
3. Should there be no radiologist specialist for the hospital, responsibility for protection measures should be entrusted to a radiologist specialist from elsewhere (engaged as a consultant).
4. It is recommended that each country form a Committee composed of medical radiologists and biophysicists, which will check whether or not the medical measures provided as protection against radiation are in accordance with the law and accepted international norms. This is (especially) recommended for countries in which such committees do not already exist.

B. Creation of a European Center for Radiobiology and Radiotherapy:

The creation of a European Center for Radiobiology and Nuclear Medicine (as a research center but not a Hospital for Radiation Therapy) would be welcomed by the majority present.

It was requested that the National Association for Medical Radiology and Nuclear Medicine in Europe appoint one delegate each to form a preparatory (or study) committee with the purpose of submitting a plan for same to this body or before the Tenth International Congress of Radiology in Montreal (in 1962). (Notice of such appointments to a committee to be sent to Professor Schinz.)—H. R. Schinz, M.D., *President*

SECOND INTERNATIONAL CONGRESS OF RADIATION RESEARCH

The Second International Congress of Radiation Research will be held in Harrogate, England, August 6–11, 1962. The Congress will be concerned with research into the physical, chemical, and biological effects of ionizing radiation. The Radiation Research Society, in cooperation with the National Academy of Sciences-National Research Council, is exploring possibilities for providing partial travel support to qualified participants. Applications must be submitted prior to February 1, 1962. Forms for this purpose are available from the Committee on Travel Grants, Room 319, 2101 Constitution Avenue, N. W., Wash-

ington 25, D. C. Further information about the Congress may be obtained from the Secretary-General, Dr. Alma Howard, Mount Vernon Hospital, Northwood, Middlesex, England.

AMERICAN SOCIETY OF X-RAY TECHNICIANS

The Thirty-fourth Annual Convention of The American Society of X-Ray Technicians is to be held at the Olympic Western Hotel, Seattle, Washington from July 7 through July 12, 1962.

Arrangements have been made for extensive Refresher Courses in technique, x-ray physics, therapy, etc. Technicians are encouraged to submit technical papers, essays, or prepare exhibits.

This is the first time that the Society is going to the Pacific Northwest. An additional attraction will be the World Fair with its extensive scientific displays. A record attendance is anticipated.

For further information please write to Mrs. Isabel H. Witters, R. T., Publicity Chairman, 314 N. E. 92nd, Seattle 15, Washington.

ANNOUNCEMENT OF GRADUATE PROGRAM IN RADIOLOGIC PHYSICS

Radiological physics graduate study and training is now available in the Department of Radiology at the Stanford University School of Medicine. The graduate study is a 2-year program open to students with a B.A. or B.S. in physics, and leads to the degree of M.A. in Medical Sciences, with specialization in Medical or Health Radiological Physics. A few fellowships will be available to qualified students. Also available is a one-year traineeship in Medical Radiological Physics for on-the-job training in the department. The traineeship, which pays an adequate stipend, is primarily intended for post-M.S. training, but consideration will be given to applicants with a B.A. or B.S. Information on both programs can be obtained from the Chairman, Department of Radiology, Stanford Medical Center, Palo Alto, California.

COURSE IN MEDICAL USES OF RADIOACTIVE ISOTOPES

A four month course will commence on Tuesday, February 6, 1962, at Queens Hospital Center and will consist of weekly five hour sessions covering lectures, laboratory exercises, and clinical management of patients.

Please apply to: Dr. Philip J. Kahan, Supervising Medical Superintendent, Queens Hospital Center, 82-68 164th Street, Jamaica 32, New York.

SHARE YOUR JOURNALS

The United States Committee of The World Medical Association is sponsoring a project to send used medical journals to physicians in Asia. Specialty journals are needed.

If you wish to participate in this doctor-to-doctor program, please write to The World Medical Association, United States Committee, Inc., 10 Columbus Circle, New York 19, New York, listing the Journal(s) you wish to contribute.

AMERICAN CLUB OF THERAPEUTIC RADIOLOGISTS

At its recent meeting on November 29, 1961 in Chicago, the American Club of Therapeutic Radiologists elected the following officers: *President*, Manuel Garcia, M.D., New Orleans; *Vice-President*, Isa-

dore Lampe, M.D., Ann Arbor; *Treasurer*, Howard Latourette, M.D., Iowa City; and *Secretary*, J. A. del Regato, M.D., Colorado Springs.

EASTERN CONFERENCE ON RADIOLOGY

The Eastern Conference of Radiology will be held in New York City at the Waldorf-Astoria Hotel on Thursday, Friday and Saturday, March 29, 30 and 31, 1962 preceding the Forty-fourth Annual Meeting of the American Radium Society. The New York Roentgen Society will be the host for this Conference.

There will be a Cocktail Party and Reception early Thursday evening, March 29, followed by a Theater Party. On Friday, March 30, there will be a luncheon and in

the evening a Dinner-Dance at the Waldorf-Astoria. An interesting social program is being planned for the wives.

The scientific sessions will run all day on Friday, and half a day on Saturday through noon. An excellent program is arranged.

For complete particulars, please write to Dr. Bernard S. Wolf, Secretary of the New York Roentgen Society, the Mount Sinai Hospital, 11 East 100 Street, New York 29, New York.



BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

PHYSICAL FOUNDATIONS OF RADIOLOGY. Third edition, revised and enlarged. By Otto Glasser, Ph.D., Professor Emeritus of Biophysics, Frank E. Bunts Educational Institute, Cleveland Clinic Foundation, Cleveland; Edith H. Quimby, Sc.D., Professor Emeritus of Radiology, College of Physicians and Surgeons, Columbia University, New York; Lauriston S. Taylor, Sc.D., Chief, Atomic and Radiation Physics Division, National Bureau of Standards, Washington, D. C.; J. L. Weatherwax, M.A., Physicist (Retired), American Oncologic Hospital, Philadelphia; and Russell H. Morgan, M.D., Professor of Radiology and Radiologist-in-Chief, Johns Hopkins University and Hospital, Baltimore. Cloth. Price, \$10.00. Pp. 503, with numerous illustrations. Publisher, Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, 49 East 33rd Street, New York 16, N. Y.

The appearance of the third, revised and enlarged, edition of this splendid book, which has become a classic of the American radiologic literature will undoubtedly be greeted with pleasure and grateful appreciation. "Physical Foundations of Radiology" since its first publication in 1944, continued to form a part of ever-increasing importance in the academic life of nearly every radiologist, and it may be unhesitatingly said that the aim originally set forth by the authors has been admirably fulfilled. This aim was to present "a compact, elementary, and essentially nonmathematical guide to radiation physics, for the physician and the student." Since only those physical principles were incorporated in the "guide" which are indispensable to the understanding of medical radiology, and since these principles were expounded in a condensed lucid manner, the book, re-edited for the second time in 1952, enjoyed unusual success.

In this third edition many timely changes may be found. Certain chapters on nonradiologic material, as for instance that on the fundamental concepts of electricity and magnetism, have been omitted, others have been recombined or re-arranged and a new

chapter on "Physics of Diagnostic Radiology," authoritatively written by Dr. Russell H. Morgan, has been added.

In the individual chapters, which number 16, likewise numerous alterations or additions may be noted. Thus the chapter on "Milestones in Radiology" has been expanded to cover the period of 1950 to 1960; the Nobel Prize winners on subjects pertaining to important discoveries in Radiation Physics and Chemistry as well as medical authors of some other important discoveries have been included; and data of the nine International Congresses of Radiology have been added. The chapters on "Roentgen-Ray Tubes," "Roentgen-Ray Circuits" and "Supervoltage Generators, High Energy Accelerators, Nuclear Reactors" have been combined into one and the material has been rewritten to encompass the latest types of apparatus. Considerable alteration and many new additions have also been made in the chapters dealing with measurements and dosage of the roentgen rays as well as of the natural and artificial radioactive elements. The last chapter contains the depth dose tables. Most of these tables have been retained unchanged from the Second Edition; in some, minor corrections have been made; and several new tables have been added either for different distances or for new types of treatment. Most important of these latter are the depth dose tables of cobalt 60, cesium 137, 4 and 8 mev. linear accelerator, and 22 mev. betatron with copper compensating filter.

The text has been excellently edited by Drs. Otto Glasser and Edith H. Quimby. The Publisher by a skillful typographical treatment of the material succeeded in producing a compact print which is easily read and has a fine artistic quality. The illustrations and diagrams are well chosen and superbly reproduced. This Third Edition of the book is enthusiastically recommended as a worthy successor of the two former eminently successful editions.

TRAIAN LEUCUTIA, M.D.

CLINICAL USE OF RADIOISOTOPES: A MANUAL OF TECHNIQUE. Second edition. Edited by Theodore Fields, M.S., F.A.C.R. (Assoc.),

Chief, Physics Section, Radioisotope Service, Veterans Administration Hospital, Hines, Illinois; Instructor in Radiology, Northwestern University Medical School; Attending Physicist, Cook County Hospital, Chicago, Illinois; Certified Medical Nuclear Physicist, American Board of Radiology; and Lindon Seed, M.D., Clinical Associate Professor of Surgery, University of Illinois College of Medicine; Director of Isotope Laboratories, Augustana Hospital, Chicago, Illinois, and Oak Park Hospital, Oak Park, Illinois; Consultant in Radioisotopes, Veterans Administration Hospital, Hines, Illinois. Cloth. Price, \$12.50. Pp. 475, with 77 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, Ill., 1961.

The revised edition of this manual continues the original purpose of providing a guide for practical application of proved techniques in Nuclear Medicine. The appearance of the second edition, only four years after the first edition, attests to the change and rapid growth in this field.

The new volume uses the same general approach as the earlier edition, but with careful modification and expansion. New authorities in various fields have been included in the group of contributors. Sections on thyroid scanning, liver function, and gastrointestinal function tests have been added.

The volume is of practical size for daily laboratory use. It is divided into four parts: routine clinical diagnostic tests, routine clinical therapy techniques, the planning and operation of a radioisotope laboratory, and a section on radiation safety with a useful group of appendices. No attempt is made to go into a detailed discussion of the physics or physiology involving the individual tests. There is generally a sufficient background description followed by detailed instructions for application and some evaluation of the technique described. No attempt is made to include every reported technique available in the literature. Discussion has wisely been limited to techniques which are of known value with wide application. For the reader who desires extension of new information supplied in these individual sections, there is a complete and well chosen bibliography following each chapter. These references in the text are sufficiently clear to

allow intelligent use of the many papers cited.

Of the changes and additions made since the first edition, the chapter on scanning is unusually good. It presents a complete analysis of the background with a step by step description of the technique to be employed. The section on gastrointestinal function tests, while very well done, is perhaps too simplified to allow the inexperienced reader to evaluate the unpredictable facets and the borderline and overlapping results one often obtains with this type of study. At this stage in the development of nuclear medicine, the reviewer would have preferred a shorter section on radioautography. There is no information on the use of radioactive material in the study of renal diseases. We feel this represents a distinct deficiency.

During the period when we feel there are too many general texts appearing on the subject of nuclear medicine, this book still represents a very useful addition. The authors' purpose to produce a manual of technique is clearly achieved. It has a distinct appeal to the casual student of nuclear medicine, but should find its greatest usefulness in the functioning radioisotope laboratory.

RAYMOND A. GAGLIARDI, M.D.

BOOKS RECEIVED

LE TRAITEMENT DES CANCERS ANO-RECTAUX PAR LA RADIOTHÉRAPIE DE CONTACT. By Jean Papillon, Professeur à la Faculté de Médecine de Lyon, Radiologiste des Hôpitaux, Chef du Service de Radiologie du Centre Léon-Bérard; Marcel Dargent, Professeur à la Faculté de Médecine de Lyon, Chirurgien des Hôpitaux, Directeur du Centre Léon-Bérard; Annick Pinet, Ancienne Interne des Hôpitaux de Lyon, Diplômée de Radiologie; and Jean-Louis Chassard, Radiologiste des Hôpitaux, Ancien Chef de Clinique à la Faculté de Médecine, Assistant de Radiologie du Centre Léon-Bérard. Paper. Pp. 167, with 3 illustrations. Masson et C^{ie}, Éditeurs, 120 Boulevard Saint-Germain, Paris (6^e), France, 1960.

PROBLEMS OF HEREDITARY CHONDRODYSPLASIAS; A ROENTGENOLOGICAL, CLINICAL AND GENETIC STUDY OF 70 CASES OF HEREDITARY CHONDRODYSPLASIAS IN 42 NORWEGIAN FAMILIES. By Andreas Hobaek, Head of the Radiological Department of the Municipal Hospital of Hauge-sund, Norway. Paper. Price, N.Kr. 45. Pp. 175, with 49 illustrations. Oslo University Press, 355 North Street, Boston 9, Mass., 1961.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY

Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Shoreham Hotel, Washington, D. C., Oct. 2-5, 1962.

AMERICAN RADIUM SOCIETY

Secretary, Dr. Charles G. Stetson, 350 Engle Street, Englewood, N. J. Annual meeting: Waldorf-Astoria Hotel, New York, N. Y., April 2-4, 1962.

RADIOLOGICAL SOCIETY OF NORTH AMERICA

Secretary, Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb.

Treasurer, Dwight Vincent Needham, 713 E. Genessee St., Syracuse, N. Y. Annual Meeting to be announced.

AMERICAN COLLEGE OF RADIOLOGY

Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois. Annual meeting: Roosevelt Hotel, New York, N. Y., Feb. 7-10, 1962.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION

Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eighth Ave., Spokane 4, Wash. Annual meeting: Chicago, Ill., June 24-28, 1962.

AMERICAN BOARD OF RADIOLOGY

Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn. The Spring 1962 examination will be held at the Terrace Hilton Hotel, Cincinnati, Ohio, June 18-22, 1962 inclusive. The deadline for filing applications was January 1, 1962. A special examination in Nuclear Medicine for Diplomates in Radiology or Therapeutic Radiology and an examination in Radiological Physics will be held if there are sufficient applications. The Fall 1962 examination will be held at the Pioneer Hotel, Tucson, Arizona, the first week in December; the deadline for filing applications is July 1, 1962. Please note that at this session Nuclear Medicine will become a mandatory part of the examination. All candidates, excluding re-examinees, who are applying for examination in Radiology or Therapeutic Radiology for the December, 1962 session or thereafter must submit a Nuclear Medicine application in addition to their basic application. This applies even to those applicants whose basic applications are on file but who will not yet have appeared for examination.

AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE

Secretary-Treasurer, Charles S. Simons, University of Michigan Hospital, Ann Arbor, Mich. Annual meeting to be announced.

TENTH INTERNATIONAL CONGRESS OF RADIOLOGY

Secretary-General, Dr. Carleton B. Peirce, Royal Victoria Hospital, Montreal 2, Quebec, Canada. Meets in Montreal, Aug. 26-Sept. 1, 1962.

EIGHTH INTER-AMERICAN CONGRESS OF RADIOLOGY

Counselor for the United States, Dr. J. A. del Regato, Penrose Cancer Hospital, 2200 North Cascade Avenue, Colorado Springs, Colorado. Meeting to be announced.

ALABAMA RADIOLOGICAL SOCIETY

Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place Alabama State Medical Association.

AMERICAN NUCLEAR SOCIETY

Executive-Secretary, Octave J. Du Temple, 86 E. Randolph St., Chicago, Ill.

ARIZONA RADIOLOGICAL SOCIETY

Secretary, Dr. Don E. Matthieson, 926 East McDowell Rd., Phoenix, Ariz. Two regular meetings a year. Annual

meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS RADIOLOGICAL SOCIETY

Secretary, Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS

Secretary, Dr. Herbert M. Stauffer, Temple University Medical Center, Philadelphia 40, Pa. Annual Meeting: University of Indiana, Indianapolis, Ind., May 19-20, 1962.

ATLANTA RADIOLOGICAL SOCIETY

Secretary, Dr. Wilson T. Edenfield, 35 Linden Ave., N.E., Atlanta 8, Ga. Meets monthly, except during three summer months, on second Friday evening.

BLOCKLY RADIOLOGICAL SOCIETY

Secretary, Dr. Samuel Finkelman, 101 S. Twentieth St., Philadelphia, Pa.

BROOKLYN RADIOLOGICAL SOCIETY

Secretary, Dr. Leslie L. Alexander, 257 New York Ave., Brooklyn 16, N. Y. Meets first Thursday of each month October through May.

BUFFALO RADIOLOGICAL SOCIETY

Secretary, Dr. R. Joseph Naples, 106 Morgan Parkway, Williamsville 21, N. Y. Meets second Monday evening each month, October to May inclusive.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY

Secretary, Dr. Joseph A. Head, 150 Marshall St., Syracuse, N. Y. Meets first Monday each month October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY

Secretary, Dr. Robert L. Freidman, Grant Hospital, Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

CENTRAL SOCIETY OF NUCLEAR MEDICINE

Secretary, Dr. Robert S. Landauer, Radiation Center Building, 1903 West Harrison St., Chicago 12, Ill.

CHICAGO ROENTGEN SOCIETY

Secretary, Dr. William F. Hutson, 5145 N. California Ave., Chicago, Ill. Meets second Thursday of each month, October to April except December at the Sheraton Hotel at 8:00 P.M.

CLEVELAND RADIOLOGICAL SOCIETY

Secretary, Dr. Ward D. Heinrich, Huron Road Hospital, Cleveland 12, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

COLORADO RADIOLOGICAL SOCIETY

Secretary, Dr. Seward Imes, 1845 High St., Denver, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

CONNECTICUT VALLEY RADIOLOGICAL SOCIETY

Secretary, Dr. James L. Krieger, 85 Jefferson St., Hartford, Conn. Meets first Friday in February and April.

DALLAS-FORT WORTH RADIOLOGICAL SOCIETY

Secretary, Dr. F. J. Bonte, 5201 Harry Hines Blvd., Dallas 35, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY

Secretary, Dr. Kenneth L. Krabbenhoft, Harper Hospital, Detroit 1, Mich. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

* Secretaries of societies are requested to send timely information promptly to the Editor.

EAST BAY ROENTGEN SOCIETY

Secretary, Dr. Dan Tucker, 454 30th St., Oakland 3, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

EAST TENNESSEE RADIOLOGICAL SOCIETY

Secretary, Dr. J. Marsh Frere, Jr., 205 Medical Arts Building, Knoxville, Tenn. Meets in January and September.

EASTERN CONFERENCE OF RADIOLOGY

Secretary, Arrangements Committee, Dr. Bernard S. Wolf, The Mount Sinai Hospital, 11 E. 100 Street, New York 29, N. Y. Annual Meeting: Waldorf-Astoria Hotel, New York, March 29-31, 1962.

EASTERN RADIOLOGICAL SOCIETY

Secretary, Dr. James F. Martin, North Carolina Baptist Hospital, Winston-Salem, N. C. Meets at Mid Pines Club, Southern Pines, N. C., April 29-May 2, 1962.

FLORIDA RADIOLOGICAL SOCIETY

Secretary, Dr. Richard D. Shapiro, 1680 Meridian Ave., Miami Beach, Fla. Meets twice annually, in the spring with the annual State Society Meeting, and in the fall.

FLORIDA WEST COAST RADIOLOGICAL SOCIETY

Secretary-Treasurer, Dr. Joseph C. Rush, 1800 Druid Rd., Clearwater, Fla.

GEORGIA RADIOLOGICAL SOCIETY

Secretary, Dr. George W. Brown, Griffin, Ga. Meets in spring and fall with Annual State Society Meeting.

GREATER MIAMI RADIOLOGICAL SOCIETY

Secretary, Dr. Carl E. Balli, 907-8 Huntington Medical Building, Miami 32, Fla. Meets monthly, third Wednesday, at 8:00 P.M. at Jackson Memorial Hospital, Miami Fla.

GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS

Secretary, Dr. William E. Powers, St. Louis, Mo.

HOUSTON RADIOLOGICAL SOCIETY

Secretary, Dr. John Douglas Reeve, Texas Medical Center Library, Jesse H. Jones Library Bldg., Houston 25, Texas. Meets last Monday each month, Seminar Room, Doctors' Club of Houston.

IDAHO STATE RADIOLOGICAL SOCIETY

Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.

ILLINOIS RADIOLOGICAL SOCIETY

Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.

INDIANA ROENTGEN SOCIETY, INC.

Secretary, Dr. David E. Wheeler, 1500 North Ritter, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

IOWA RADIOLOGICAL SOCIETY

Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

KANSAS RADIOLOGICAL SOCIETY

Secretary, Dr. Roger K. Wallace, Riley County Hospital, Manhattan, Kansas. Meets in spring with State Medical Society, and in winter on call.

KENTUCKY RADIOLOGICAL SOCIETY

Secretary, Dr. Lawrence A. Davis, 226 East Chestnut St., Louisville, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

KINGS COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. Abraham Berens, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

LOS ANGELES RADIOLOGICAL SOCIETY

Secretary, Dr. Saul Heiser, Los Angeles, Calif. Meets second Wednesday of month in September, November, January, March and June at Los Angeles County Medical Association Building, Los Angeles.

MAINE RADIOLOGICAL SOCIETY

Secretary, Dr. Albert A. Poulin, Thayer Hospital, Water-

ville, Maine. Meets in June, September, December and April.

MARYLAND RADIOLOGICAL SOCIETY

Secretary, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore 17, Md.

MEMPHIS ROENTGEN SOCIETY

Secretary, Dr. Irving K. Ettman, Kennedy V.A. Hospital, Department of Radiology, Memphis 15, Tenn. Meets first Monday of each month at John Gaston Hospital.

MIAMI VALLEY RADIOLOGICAL SOCIETY

Secretary, Dr. William D. Roberts, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.

MID-HUDSON RADIOLOGICAL SOCIETY

Secretary, Dr. Joseph Sorrentino, St. Francis Hospital, Poughkeepsie, N. Y. Meets 8:30 P.M., fourth Wednesday each month, September to May.

MILWAUKEE ROENTGEN RAY SOCIETY

Secretary, Dr. Abraham Marck, Mayfair Professional Bldg., Milwaukee 13, Wis. Meets monthly on fourth Monday, October through May, at University Club.

MINNESOTA RADIOLOGICAL SOCIETY

Secretary, Dr. Donald H. Peterson, 853 Medical Arts Bldg., Minneapolis 2, Minn. Meets three times annually, in fall, winter and spring.

MISSISSIPPI RADIOLOGICAL SOCIETY

Secretary, Dr. Jack K. Goodrich, University Medical Center, Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 P.M.

MONTANA RADIOLOGICAL SOCIETY

Secretary, Dr. J. K. Boughn, 35 11th Ave., Helena, Montana. Meets at least once a year.

NASSAU RADIOLOGICAL SOCIETY

Secretary, Dr. Robert Tugendhaft, 100 Nowbridge Rd., Hicksville, N. Y. Meets second Tuesday of the month in February, April, June, October and December.

NEBRASKA STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Richard Bunting, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Nebraska. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEW ENGLAND ROENTGEN RAY SOCIETY

Secretary, Dr. Robert E. Wise, 605 Commonwealth Ave., Boston 15, Mass. Meets third Friday of each month, October through April at The Longwood Towers, Brookline, Mass.

NEW HAMPSHIRE ROENTGEN RAY SOCIETY

Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.

NEW YORK ROENTGEN SOCIETY

Secretary, Dr. Bernard S. Wolf, Mt. Sinai Hospital, New York, N. Y. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M.

NORTH CAROLINA RADIOLOGICAL SOCIETY

Secretary, Dr. A. B. Croom, 624 Quaker Lane, High Point, N. C. Meets in the spring and fall each year.

NORTH DAKOTA RADIOLOGICAL SOCIETY

Secretary, Dr. John Jestadt, Depuy-Sorkness Clinic, Jamestown, North Dakota. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.

NORTH FLORIDA RADIOLOGICAL SOCIETY

Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.

NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY

Secretary, Dr. Lester I. Citrin, St. Mary's Hospital, Troy, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.

NORTHERN CALIFORNIA RADIOLOGICAL SOCIETY

Secretary, Dr. Rob H. Kirkpatrick, 1219 28th St., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

NORTHWESTERN OHIO RADIOLOGICAL SOCIETY

Secretary, Dr. George Asahina, 421 Michigan St., Toledo, Ohio.

OHIO STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Chapin Hawley, 927 Carew Tower, Cincinnati, Ohio. Annual meeting to be announced.

OKLAHOMA STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Simon Pollack, Utica Square Medical Center, Tulsa, Okla. Meets in January, May and October.

OREGON RADIOLOGICAL SOCIETY

Secretary, Dr. George R. Satterwhite, Willamette Falls Community Hospital, 15th and Division, Oregon City, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

ORLEANS PARISH RADIOLOGICAL SOCIETY

Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY

Secretary, Dr. John N. Burkey, 555 Dental Bldg., Seattle, Wash. Annual meeting: Seattle, Washington.

PACIFIC ROENTGEN SOCIETY

Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco 8, Calif. Meets annually during meeting of California Medical Association.

PENNSYLVANIA RADIOLOGICAL SOCIETY

Secretary, Dr. Frederick R. Gilmore, Clearfield Hospital, Clearfield, Pa. Annual meeting: Pocono Manor Inn, May 25-26, 1962.

PHILADELPHIA ROENTGEN RAY SOCIETY

Secretary, Dr. Robert B. Funch, Department of Radiology, Germantown Hospital, Philadelphia 44, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY

Secretary, Dr. Ross H. Smith, St. Margaret Memorial Hospital, Forty-Sixth St., Pittsburgh 1, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

RADIOLOGICAL SECTION, BALTIMORE MEDICAL SOCIETY

Secretary, Dr. James K. V. Willson, 1100 N. Charles St., Baltimore 1, Md. Meets third Tuesday each month, September to May, inclusive.

RADIOLOGICAL SOCIETY OF GREATER CINCINNATI

Secretary, Dr. William C. Duffey, Cincinnati, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

RADIOLOGICAL SOCIETY OF HAWAII

Secretary, Dr. G. J. Liese, Queen's Hospital, Honolulu, Hawaii. Meets third Monday of each month at 7:30 P.M.

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY

Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

RADIOLOGICAL SOCIETY OF KANSAS CITY

Secretary, Dr. Arthur B. Smith, 800 Argle Bldg., Kansas City, Mo. Meets third Thursday of each month.

RADIOLOGICAL SOCIETY OF LOUISIANA

Secretary, Dr. Robyn Hardy, 4324 Magnolia St., New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

RADIOLOGICAL SOCIETY OF NEW JERSEY

Secretary, Dr. George H. Burke, 601 Grand Ave., Asbury Park, N. J. Meets at Atlantic City at time of State Medical Society meeting and in November in Newark, N. J.

RADIOLOGICAL SOCIETY OF THE STATE OF NEW YORK

Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y. Annual meeting to be announced.

RADIOLOGICAL SOCIETY OF SOUTH DAKOTA

Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

RADIOLOGICAL SOCIETY OF SOUTHERN CALIFORNIA

Secretary, Dr. Robert Scanlan, St. Vincent's Hospital, Los Angeles, Calif.

REDWOOD EMPIRE RADIOLOGICAL SOCIETY

Secretary, Dr. Lee E. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

RICHMOND COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y.

Secretary, Dr. Robert H. Greenlaw, 260 Crittenden Blvd., Rochester 20, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting: Denver Hilton Hotel, Denver, Colo., Aug. 16-18, 1962.

SAN ANTONIO-MILITARY RADIOLOGICAL SOCIETY

Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

SAN DIEGO RADIOLOGICAL SOCIETY

Secretary, Dr. Stanley A. Moore, 2466 First Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

SAN FRANCISCO RADIOLOGICAL SOCIETY

Secretary, Dr. Walter Coulson, San Francisco General Hospital, San Francisco 8, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 13, Calif.

SECTION ON RADIOLOGY, CALIFORNIA MEDICAL ASSOCIATION

Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

SECTION ON RADIOLOGY, CONNECTICUT STATE MEDICAL SOCIETY

Secretary, Dr. Wayne P. Whitcomb, Hospital of St. Raphael, New Haven, Conn. Meetings are held bi-monthly.

SECTION ON RADIOLOGY, MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA

Secretary, Dr. William E. Sheely, 1746 K St., N.W., Washington 6, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

SECTION ON RADIOLOGY, ILLINOIS STATE MEDICAL SOCIETY

Secretary, Dr. William Meszaros, 1825 W. Harrison St., Chicago, Ill.

SECTION ON RADIOLOGY, SOUTHERN MEDICAL ASSOCIATION

Secretary, Dr. Seymour Ochsner, Ochsner Clinic, 3503 Prytania St., New Orleans 15, La. Annual meeting to be announced.

SHREVEPORT RADIOLOGICAL CLUB

Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY

Secretary, Dr. Richard G. Lester, 412 Union St., S.E., Minneapolis 14, Minn. Annual meeting to be announced.

SOCIETY OF NUCLEAR MEDICINE

Secretary, Dr. Robert W. Lackey, 452 Metropolitan Bldg., Denver 2, Colo. *Administrator*, Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Baker Hotel, Dallas, Texas, June 27-30, 1962.

SOUTH BAY RADIOLOGICAL SOCIETY

Secretary, Dr. Stanford B. Rossiter, 1111 University Dr., Menlo Park, Calif. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY

Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

SOUTHERN RADIOLOGICAL CONFERENCE

Secretary, Dr. Marshall Eskridge, Mobile Infirmary
P.O. Box 4097, Mobile, Ala.

SOUTHWESTERN RADIOLOGICAL SOCIETY

Secretary, Dr. Ralph S. Clayton, 1501 Arizona, Bldg.
2-A, El Paso, Texas. Meets second Tuesday of each month.

TENNESSEE RADIOLOGICAL SOCIETY

Secretary, Dr. B. M. Brady, St. Joseph Hospital, Memphis, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

TEXAS RADIOLOGICAL SOCIETY

Secretary, Dr. R. P. O'Bannon, 402 Professional Bldg.,
1216 Pennsylvania Ave., Fort Worth 4, Texas. Annual meeting: Austin, Texas, Jan. 19 and 20, 1962.

TRI-STATE RADIOLOGICAL SOCIETY

Secretary, Dr. John H. Marchand, Jr., Welborn Clinic,
420 Cherry St., Evansville, Ind. Meets third Wednesday of Oct., Jan., March and May, 8:00 P.M., Elks Club in Evansville.

UNIVERSITY OF MICHIGAN DEPARTMENT OF ROENTGENOLOGY STAFF MEETING

Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

UPPER PENINSULA RADIOLOGICAL SOCIETY

Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

UTAH STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Richard Y. Card, St. Mark's Hospital, Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

VIRGINIA RADIOLOGICAL SOCIETY

Secretary, Dr. Powell G. Dillard, Jr., 715 Church Street,
Lynchburg, Va. Meets annually in October.

WASHINGTON STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Joseph T. Houk, 14303 Ambaum Blvd.,
Seattle 66, Wash. Meets third Monday of each month from September through April at the University of Washington Medical School.

WEST VIRGINIA RADIOLOGICAL SOCIETY

Secretary, Dr. Karl J. Myers, The Myers Clinic-Broadus Hospital, Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

WESTCHESTER RADIOLOGICAL SOCIETY

Secretary, Dr. Anthony A. Maglione, Westchester Academy of Medicine, Section on Radiology, Purchase, N. Y. Meets on third Tuesday of January and October and on two other dates.

WISCONSIN RADIOLOGICAL SOCIETY

Secretary, Dr. Howard G. Bayley, 116 Iroquois Parkway,
Beaver Dam, Wis. Annual meeting each spring in various places.

CUBA, MEXICO, PUERTO RICO AND CENTRAL AMERICA

ASOCIACIÓN DE RADIOLOGOS DE CENTRO AMERICA Y PANAMÁ. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.

Secretary-General, Dr. Julio Toriello, 11 Calle 2-37, Zona 1, Guatemala. Meets annually in a rotating manner in the six countries.

SOCIEDAD DE RADIOLOGÍA DE EL SALVADOR

Secretary, Dr. Rafael Vaga Gómez.

SOCIEDAD DE RADIOLOGÍA DE GUATEMALA

Secretary, Dr. Carlos E. Escobar, 9ª Calle A 0-05, Zona 1, Guatemala.

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPIA CUBANA

Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

SOCIEDAD COSTARRICENSE DE RADIOLOGIA

Secretary, Dr. James Fernández Carballo, Apartado VIII,
San José, Costa Rica.

SOCIEDAD MEXICANA DE RADIOLOGÍA, A. C.

Calle del Oro No. 15, México 7, D. F.

Secretary-General, Dr. E. Alvarez Hernández. Meets first Monday of each month.

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA

Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

SOCIEDAD RADIOLOGICA PANAMEÑA

Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

SOCIEDAD RADIOLOGICA DE PUERTO RICO

Secretary, Dr. César E. Rosa-Perez, Fondo del Seguro del Estado, Parada 1, San Juan 8, Puerto Rico. Meets second Thursday of each month at 8:00 P.M. at the Puerto Rico Medical Association Bldg. in San Juan.

BRITISH COMMONWEALTH OF NATIONS

ASSOCIATION OF RADIOLOGISTS OF THE PROVINCE OF QUEBEC

Secretary, Dr. Odilon Raymond, 5400 Blvd. Gouin,
Quebec, Montreal, Que. Meets four times a year.

BRITISH INSTITUTE OF RADIOLOGY

Honorary Secretary, Dr. R. D. Hoare, 32 Welbeck St.,
London, W. 1. Meets monthly from October until May.

EDMONTON AND DISTRICT RADIOLOGICAL SOCIETY

Secretary, Dr. S. C. Windle, 105 Northgate Bldg.,
Edmonton, Alberta. Meets first Tuesday of each month, October to May.

FACULTY OF RADIOLOGISTS

Honorary Secretary, Dr. C. J. Hodson, 47 Lincoln's Inn
Fields, London, W.C.2, England. Annual meeting: Ham-
mersmith Hospital and the Postgraduate Medical School,
London, June 15-16, 1962.

SECTION OF RADIOLOGY OF THE ROYAL SOCIETY OF MEDICINE (CONFINED TO MEDICAL MEMBERS)

Meets third Friday each month at 4:45 P.M. at the Royal
Society of Medicine, 1 Wimpole St., London, W. 1.

CANADIAN ASSOCIATION OF RADIOLOGISTS

Honorary Secretary, Dr. Robert G. Fraser, *Associate Hon-
orary Secretary*, Dr. Jean-Louis Léger, 1555 Summerhill
Ave., Montreal 25, Que. Annual meeting: Marlborough
Hotel, Winnipeg, Man., Jan. 22-24, 1962.

MONTREAL RADIOLOGICAL STUDY CLUB

Secretary, Dr. F. McConnell, 1650 Cedar Ave., Montreal,
Quebec. Meets first Tuesday evening, October to April.

SECTION OF RADIOLOGY, CANADIAN MEDICAL ASSOCIATION

Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

SOCIÉTÉ CANADIENNE-FRANÇAISE D'ELECTRO-RADIOLOGIE MÉDICALE

General Secretary, Dr. Maurice Dufresne, 1560 Sher-
brooke (East), Montreal, Canada. Meets third Saturday
each month.

TORONTO RADIOLOGICAL SOCIETY

Secretary, Dr. Wallace M. Roy, St. Joseph's Hospital,
30 The Queensway, Toronto 3, Ontario. Meets second
Monday of each month September through May.

COLLEGE OF RADIOLOGISTS OF AUSTRALIA

Honorary Secretary, Dr. E. A. Booth, c/o British Medical
Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

SOUTH AMERICA

ASOCIACIÓN ARGENTINA DE RADIOLOGÍA

Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151,
Córdoba, Argentina. Meetings held monthly.

ATENEO DE RADIOLOGIA

Secretary, Dr. Victor A. Añños, Instituto de Radiología,
Santa Fe 3100, Rosario, Argentina. Meets monthly on
second and fourth Fridays at 7:00 P.M. in the Hospital
Nacional del Centenario, Santa Fe 1300, Rosario.

COLÉGIO BRASILEIRO DE RADIOLOGIA

Secretary-General, Dr. Tede Eston de Eston, Caixa Postal
5984, São Paulo, Brazil.

SOCIEDAD ARGENTINA DE RADIOLOGÍA, JUNTA CENTRAL, BUENOS AIRES

Secretary, Dr. Edgardo O. Olcese, Santa Fé 1171, Buenos Aires. Meetings are held monthly.

SOCIEDAD BOLIVIANA DE RADIOLOGÍA

Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

SOCIEDADE BRASILEIRA DE RADIOLOGIA

Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

SOCIEDADE BRASILEIRA DE RADIOTERAPIA

Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

SOCIEDAD CHILENA DE RADIOLOGÍA

Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

SOCIEDAD COLOMBIANA DE RADIOLOGIA

Secretary, Dr. Alberto Mejía Diazgranados, Carrera 13, No. 25-31, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

SOCIEDAD ECUATORIANA DE RADIOLOGÍA Y FISIOTERAPIA

Secretary, Dr. Publio Vargas P., Casilla 1242, Guayaquil, Ecuador.

SOCIEDAD PARAGUAYA DE RADIOLOGÍA

Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

SOCIEDAD PERUANA DE RADIOLOGIA

Secretary, Dr. Luis Pinillos Ganoza, Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

SOCIEDAD DE RADIOLOGIA DEL ATLANTICO

Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

SOCIEDAD DE RADIOLOGÍA, CANCEROLOGÍA Y FÍSICA MÉDICA DEL URUGUAY

Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

SOCIEDADE DE RADIOLOGIA DE PERNAMBUCO

Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

SOCIEDAD DE ROENTGENOLOGIA Y MEDICINA NUCLEAR DE LA PROVINCIA DE CÓRDOBA

Secretary-General, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

SOCIEDAD VENEZOLANA DE RADIOLOGÍA

Secretary-General, Dr. Rubén Merinfeld, Apartado No. 9362, Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

CONTINENTAL EUROPE

ÖSTERREICHISCHE RÖNTGEN-GESELLSCHAFT

President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

SOCIÉTÉ BELGE DE RADIOLOGIE

General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets in February, March, May, June, October, November and December.

SOCIÉTÉ FRANÇAISE D'ELECTRORADIOLOGIE MÉDICALE, and its branches: SOCIÉTÉ DU SUD-OUEST, DU LITTORAL MÉDITERRANÉEN, DU CENTRE ET DU LYONNAIS, DU NORD, DE L'OUEST, DE L'EST, ET D'ALGER ET D'AFRIQUE DU NORD. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris.

Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 8^e, France.

ČESKOSLOVENSKÁ SPOLEČNOST PRO ROENTGENOLOGII A RADIOLOGII

Secretary, Dr. Robert Poch, Praha 12, Šrobárova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

DEUTSCHE RÖNTGENGESELLSCHAFT

Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut. Lagenbeckstr. 1, Mainz, Germany. Annual meeting to be announced.

SOCIETÀ ITALIANA DI RADIOLOGIA MEDICA E DI MEDICINA NUCLEARE

Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

NEDERLANDSE VERENIGING VOOR ELECTROLOGIE EN RÖNTGENOLOGIE

Secretary, Dr. J. R. von Ronnen, Violonweg 14, den Haag, Netherlands.

SCANDINAVIAN ROENTGEN SOCIETIES

The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

SOCIEDAD ESPAÑOLA DE RADIOLOGÍA Y ELECTROLOGÍA MÉDICAS Y MEDICINA NUCLEAR

Secretary, Dr. D. Aureo Gutierrez Churruga, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

SCHWEIZERISCHE GESELLSCHAFT FÜR RADIOLOGIE UND NUKLEARMEDIZIN (SOCIÉTÉ SUISSE DE RADIOLOGIE ET DE MÉDECINE NUCLÉAIRE)

Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

INDIA

INDIAN RADIOLOGICAL ASSOCIATION

Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.



ABSTRACTS OF RADIOLOGICAL LITERATURE

INDEX TO ABSTRACTS

ROENTGEN DIAGNOSIS

NECK AND CHEST

- CUMMING, G. R., and FINKEL, K.: Intracardiac myxoma involving the right and left atria in a young patient..... 218

ABDOMEN

- SOMMER, A. W., and STEVENSON, C. L.: Hiatal hernia; an evaluation of diagnostic procedures..... 218
EXTON-SMITH, A. N., and OSBORNE, G.: Barium studies in the aged..... 218
MARSHAK, R. H., and ELIASOPOULOS, J.: Inflammatory lesions of the small bowel secondary to colonic diverticulitis..... 219
SMULEWICZ, J., and EPSTEIN, B. S.: Radiologic changes associated with acute pseudomembranous enterocolitis..... 219
ANTOINE, M. *et al.*: Radiology of congenital megacolon..... 220
HILLEMANN, P., MIALARET, J., and BOUTELIER, D.: Duodenal exclusion and osteomalacia in gastrectomized patients..... 220
NORMAN, A., and SAGHATOLESAMI, M.: Oral extrahepatic cholangiography: a simple reliable technic..... 221
KAPLAN, A. A. *et al.*: Percutaneous transhepatic cholangiography..... 221
LEGER, L.: Visualization of dilatation of the canal of Wirsung; an attempt at classification..... 222
MICHEL, J.: Radiologic study of mucoviscidosis of the pancreas..... 222

GYNECOLOGY AND OBSTETRICS

- HEAGY, F. C., and SWARTZ, D. P.: Localizing the placenta with radioactive iodinated human serum albumin..... 223
HAMILL, G. C., JARMAN, J. A., and WYNNE, M. D.: Fetal effects of radioactive iodine therapy in a pregnant woman with thyroid cancer..... 223
LEWIS, R. H.: Foetus in foetu and the retroperitoneal teratoma..... 223
WELLS, J., and STEER, C. M.: Relationship of leukemia in children to abdominal irradiation of mothers during pregnancy..... 224

GENTOURINARY SYSTEM

- TRUC, E. *et al.*: Radiologic examination in traumas of kidney..... 224
HINMAN, F., JR.: Peripelvic extravasation during intravenous urography, evidence for an additional route for backflow after ureteral obstruction..... 224
HARROW, B. R., and SLOANE, J. A.: Pyelorenal extravasation during excretory urography..... 225
MONACO, H., O'CONNOR, T. E., and MOUREU, R. S.: An ectopic ureterovulvar opening in a double ureter malformation..... 225
PORIES, W. J., McDONALD, D. F., and HINSHAW, J. R.: A calibrated radiopaque Penrose drain..... 225
GROUSTREMES, V., BOYARSKY, S., and NEWMAN, H. R.: Fatal air embolism following presacral air insufflation; occurrence despite manometric control..... 226
SCHMIDLAPP, C. J., II: Respiratory (cardiac) arrest after retrograde pyelography with neomycin-containing medium..... 226
FELTON, L. M.: Should intravenous pyelography be a routine procedure for children with cryptorchism and hypospadias?..... 227
STEVENSON, J., MacGREGOR, A. M., and CONNELLY, P.: Calcification of the adrenal glands in young children; a report of three cases with a review of the literature..... 227

NERVOUS SYSTEM

- SVIEN, H. J., and BAKER, H. L., JR.: Roentgenographic and surgical aspects of vascular anomalies of the spinal cord..... 227
CURTISS, P. H., JR., and COLLINS, W. F.: Spinal-cord tumor—a cause of progressive neurological changes in children with scoliosis; a report of three cases..... 228
BLIGH, A. S.: Diastematomyelia..... 228

SKELETAL SYSTEM

- VAN CANGHEM, P., and SCHIRREN, C. G.: The influence of radiation quality on inhibition of growth by irradiation of the tarso-metatarsal joints of chicks..... 228
HAYES, J. T.: Cystic tuberculosis of the proximal tibial metaphysis with associated involvement of the epiphysis and epiphyseal plate; a report of two cases..... 228

- BEZES, H.: Osseous lesions of mycetoma of the foot..... 229
- VARADARAJAN, M. G.: Actinomycosis of bone..... 229
- MACKENZIE, A. *et al.*: Mortality from primary tumours of bone in England and Wales.... 229
- PHALEN, G. S., and DICKSON, J. A.: Spondylolisthesis and tight hamstrings..... 230
- CHILDE, A. E., and TUCKER, F. R.: Spondylarthritis in infants and children..... 230
- VESPIGNANI, L., and ZORAT, G.: Arthrographic diagnosis of discoid meniscus (4 cases)..... 230
- BLOOD AND LYMPH SYSTEM
- ROY, P., JUTRAS, A., and LONGTIN, M.: Extra large field angiography: technique and results..... 230
- PEDRO-BOTET, J.: Diagnostic use of splenoportography in the Cruveilhier-Baumgarten syndrome..... 231
- PIPER, D. W.: A radiographic study of the portal and hepatic venous systems in cirrhosis of the liver..... 231
- ASSCHER, A. W., WILSON, C., and ANSON, S. G.: Sensitisation of blood-vessels to hypertensive damage by x-irradiation..... 232
- GARCIA, N. A., III *et al.*: Findings on retrograde femoral arteriography in choriocarcinoma..... 232
- JACKSON, L. *et al.*: The diagnostic value of lymphangiography..... 232
- GENERAL
- MORGAN, R. H.: The measurement of radiant energy levels in diagnostic roentgenology... 233
- RADIATION THERAPY
- YANGUAS, M. G.: Treatment of peritendinitis (bursitis) with roentgen rays; review of 285 cases..... 234
- PELÚ, G.: Consideration of radiotherapy of Wilms' tumor; with particular attention to the long term results of treatment of the primary site and of the metastasis..... 234



ROENTGEN DIAGNOSIS

NECK AND CHEST

CUMMING, G. R., and FINKEL, K. Intracardiac myxoma involving the right and left atria in a young patient. *J. Pediat.*, Apr., 1961, 58, 559-567. (Address: G. R. Cumming, The Children's Hospital of Winnipeg, 685 Bannatyne Avenue, Winnipeg 3, Manitoba, Canada.)

Although over 200 cases of atrial myxomas have been reported in the literature, only 9 have occurred in children under sixteen years of age. The authors report a case of a nine year old boy who had intermittent embolic episodes to the extremities and the brain.

At autopsy, a large myxoma (9.0×4.2×3.0 cm.) was found on a pedicle arising from the left side of the atrial septum near the foramen ovale; it filled the entire left atrium, extended through the mitral valve to fill part of the left ventricle, and also extended through the foramen ovale to form a mass 3.5×2.0×1.0 cm. in the right atrium. The left internal carotid and middle cerebral vessels were filled completely with myxomatous tissue.

The most notable feature of left atrial myxoma in the young is the high incidence of cerebral emboli. Any embolic episode in a pediatric patient should suggest the possibility of an atrial myxoma and angiocardiology should be considered despite the absence of cardiac symptoms and signs. In the young patient, atrial myxoma may closely simulate rheumatic heart disease. The clinical picture may be that of mitral regurgitation rather than stenosis as is usually emphasized in adult patients.

In apparent cases of mitral valve disease, left atrial myxoma is suggested when: (a) there is no history of rheumatic fever; (b) the intensity of the murmurs changes rapidly and often; (c) the murmurs change with posture; (d) postural symptoms occur; (e) the course is relentlessly downhill; (f) there is severe disease with persistent sinus rhythm; (g) there are emboli in the absence of atrial fibrillation; and (h) the clinical picture resembles mitral stenosis but a systolic apical murmur is frequently heard.

Right atrial myxomas are less common in the 9 cases of atrial myxomas in children previously reported in the literature. In only 2 cases did the lesion arise from the right atrium. Right atrial myxoma is suggested: (a) in isolated tricuspid valve disease; (b) in unusual cases of right heart failure; (c) when there are postural symptoms; and (d) in cases with recurrent pulmonary emboli.—*Eugene C. Klatte, M.D.*

ABDOMEN

SOMMER, ARNO W., and STEVENSON, CHARLES L. Hiatal hernia; an evaluation of diagnostic

procedures. *Am. J. Digest. Dis.*, 1961, 6, 412-422. (Address: A. W. Sommer, Scott and White Clinic, Temple, Tex.)

The diagnosis of hiatal hernia was made on 137 patients during a period of thirty months. It was recorded as a clinical reason for examination in only 68 of these patients.

Of the 137 patients, 68 had hernias 4 to 5 cm. in size (small); 55, 6 to 7 cm. (medium); and 14, 8 cm. or larger (large.) The sliding type of herniation was observed 129 times, while the paraesophageal (eccentric) type was demonstrated only 8 times. Seventy-four of the patients were men, 63 were women. The ages ranged from thirty-six to eighty-three years, the average being sixty. Eighty-one per cent of the patients were between forty and sixty-nine years of age. Women who were examined less than one year post partum were excluded from the study.

The diagnostic procedures carried out were barium swallowing with both fluoroscopy and roentgenography in: right anterior oblique recumbent position (roentgenograms); Trendelenburg position (fluoroscopy and roentgenograms); and angle board position (roentgenograms). In only 37 of the patients were the findings positive for herniation at the esophageal hiatus by all roentgenologic methods. Study of the esophagus while the patient was swallowing barium enabled a diagnosis of hiatus hernia in 44 of the 137 instances. A comprehensive table is given listing the findings with the four methods of examination in the 137 patients.

There is a detailed description of the angle board technique used, with the angle being 34 degrees.

The authors conclude that the hernias are best demonstrated if the stomach contains a moderate amount of barium and that, regardless of the four methods used, insufficient barium frequently results in failure to reveal herniation. A hiatal hernia associated with a high transverse stomach is difficult to visualize by any method. The angle board technique yielded very good results and has now been adopted as a routine procedure for detecting hiatal herniation.

In the conclusion the authors state that large hiatal hernias can be demonstrated by all diagnostic methods; no one diagnostic procedure can be relied upon to reveal small hernias; examination of the patient in the upright position is of little value for visualizing hiatal herniation; and the highest diagnostic accuracy results from the use of the angle board technique.—*C. Peter Truog, M.D.*

EXTON-SMITH, A.N., and OSBORNE, G. Barium studies in the aged. *Brit. M. J.*, 1961, 2, 1799-1802. (From: Whittington Hospital, London, England.)

As the possibility of treatment in the field of geriatrics increases, more and more elderly patients

are submitted to roentgenologic examinations. Administration of barium meals and enemas may be difficult in such patients. The authors have reviewed a series of 102 barium meal and 46 barium enema examinations to determine in how many the results were of practical value and in how many they were merely of academic interest. All the patients were seventy or more years old, the oldest ninety-three years.

The authors conclude that the barium meal examinations were surprisingly valuable. On the other hand they feel that the number of barium enema examinations might well be reduced, particularly in view of the distressing preparation involved and the occasional complications that occur. They are inclined to agree with Haggie's conclusions that it is highly improbable that a patient complaining only of colonic symptoms, without blood in the stools and showing no abnormal physical signs and no abnormality on rectal examination or sigmoidoscopy will be found to have carcinoma of the colon if a barium enema is given—*A. E. Childe, M.D.*

MARSHAK, RICHARD H., and ELIASOPH, JOAN.

Inflammatory lesions of the small bowel secondary to colonic diverticulitis. *Am. J. Digest. Dis.*, 1961, 6, 423-428. (Address: R. H. Marshak, 1075 Park Ave., New York 28, N. Y.)

The authors report 3 cases of sigmoid diverticulitis in which roentgen-detectable alterations in the small intestine were observed.

Case I was a man fifty-three years of age who had repeated episodes of dull, aching, left lower quadrant pain over a period of several years. Barium enema examination during one of the episodes revealed a few diverticula associated with mild spasm in the sigmoid. There was no evidence of an extrinsic mass or perforation. The remainder of the colon was normal. Because the diverticula appeared quiescent, a small intestinal series was performed. The pertinent findings were limited to a short 4 cm. segment of distal jejunum adjacent to the sigmoid. The lumen was moderately narrowed and the mucosal folds were slightly thickened and distorted. The jejunum in this region was fixed in position and maintained a constant relation to the sigmoid, separated by 1 cm. of intervening soft tissue. The jejunum proximally was slightly dilated. The alterations were interpreted as being due to pericolicitis occasioned by diverticulitis, with secondary involvement of a segment of the jejunum. After two weeks of antibiotic therapy, a repeat small intestinal series revealed no abnormalities.

Case II was a female sixty-eight years of age who had severe left lower quadrant pain with fever and distention of the abdomen. A plain roentgenogram of the abdomen revealed slight small intestine distention; air and fecal material outlined portions of

the colon. Barium enema examination demonstrated narrowing of the sigmoid for about 5 cm. with a moderate number of diverticula in this region. The mucosal folds in this area were distorted and thickened. There was some rigidity of the medial wall of the sigmoid with evidence of extrinsic pressure, indicating a mass. Adjacent to the pericolic mass, small-intestine loops were visualized (because of reflux through the ileocecal valve), showing slight narrowing of the lumen, increased secretions, thickening and blunting of the folds and a relatively fixed position. Their impression was sigmoid diverticulitis, abscess formation and secondary inflammation of several loops of adjacent small intestine.

Case III was a fifty year old female with repeated attacks of left lower quadrant pain, fever, tenderness and a palpable mass in this region. Repeated barium studies revealed narrowing of the sigmoid lumen, numerous diverticula, thickening of the mucosal folds, irritability and spasm. A small intestine series had never been performed. After several further episodes of diverticulitis, a repeat barium enema study was done. At this time, barium entered the jejunum via a fistula from the sigmoid. The sigmoid itself was spastic, irritable and narrowed and showed thickened mucosal folds. The diverticula were again demonstrated. After a diversion colostomy, the fistula was resected, the jejunum repaired and finally the inflamed sigmoid removed.

Roentgenograms showing the changes described in each of the patients are reproduced.—*C. Peter Truog, M.D.*

SMULEWICZ, JACOB, and EPSTEIN, BERNARD S.

Radiologic changes associated with acute pseudomembranous enterocolitis. *Radiol. clin.*, 1961, 30, 110-117. (From: Department of Radiology, The Long Island Jewish Hospital, New Hyde Park, Long Island, N. Y.)

The authors report 6 patients who came to necropsy. There is an attempt to correlate the roentgenologic changes with the clinical picture. Previous gastrointestinal surgery had been performed in 4 of the patients and all of them had received antibiotics, such as achromycin, erythromycin and terramycin in therapeutic doses. The patients had received this medication for a period of four to ten days.

Acute pseudomembranous enterocolitis is usually characterized by a sudden, rapidly progressive and overwhelming shock with fatal termination. Vomiting, distention, oliguria and a variable diarrhea appeared. The diarrhea may be relatively late in onset and is sometimes absent. Although abdominal cramps may be severe, nontenderness to palpation is present. There is difficulty in distinguishing this condition from postoperative intestinal obstruction, peritonitis or ileus. A mild form with a distinctly

lower mortality, and which may go unrecognized, also exists.

The pathologic changes due to acute pseudomembranous enterocolitis occur most often in the ileum and colon, less so in the jejunum, and infrequently in the duodenum and stomach. Diffuse bowel dilatation, hyperemia of the serosa, together with a fibrinous, loosely adherent light or dark membrane, overlying eroded, congested mucosa in plaques or as an extensive coating over several feet of intestine are the principal alterations. Microscopic examination discloses absent or necrotic mucosa and a fibropurulent exudate forming a loosely adherent membrane, within which bacterial colonies may be identified. The submucosa becomes edematous, hyperemic and infiltrated, while the muscular coats present a variable degree of inflammation and necrosis.

The 2 nonsurgical patients were a nine year old girl with acute lymphatic leukemia and a seventy-six year old female. The elderly lady had azotemia due to nephrosclerosis.

The 4 patients operated upon had surgery because of intestinal obstruction due to carcinoma of the ascending colon in 1 and diverticulosis in 2 others. The fourth patient had an oophorectomy as a palliative procedure for breast carcinoma. This patient also had diffuse peritoneal metastases at the time of surgery.

The predominant roentgenologic change seen in all 6 patients was diffuse small bowel distention together with a lesser degree of colonic dilatation. In 2, a definite ladder pattern with fluid level was present and the clinical as well as the roentgenologic diagnosis was slanted toward small bowel obstruction. In 2 others the changes were attributed to postoperative ileus and peritonitis. In the remaining 2, the changes observed on the scout abdominal roentgenograms were minor, even though extensive disease was found at necropsy.

The authors believe that while pseudomembranous enterocolitis may occur without previous surgery, it is seen more often in postoperative patients. Bowel obstruction may be a predisposing factor. The role of antibiotic medication in the production of this disease still is not established conclusively but there is much evidence that supports its significance. The roentgenologic manifestations are nonspecific and reflect a widely variable ileus so pronounced in some as to simulate small intestinal obstruction.

The authors conclude that there is no correlation between the extent and severity of the disease and the roentgenologic pattern of gaseous bowel dilatation.—*C. Peter Truog, M.D.*

ANTOINE, M., MANCIAUX, M., PRÉVOT, J., and DE KERSAUSON, M. C. (Nancy, France.) La radiologie du mégacolon congénital. (Radiology of congenital megacolon.) *J. de radiol.*,

d'électrol., et de méd. nucléaire, Mar.-Apr., 1961, 42, 101-108.

The authors stress the neurogenic etiologic factor in congenital megacolon. They also stress the importance of ruling out megacolon secondary to other causes.

A ganglionic dystonia, a term proposed by Laurence, describes the histologic basis for the diagnosis of this condition, which is a disorder of the neurovegetative system. There is a striking decrease or total absence of the cells of the visceral ganglia at the level of the involved segment. Tissue biopsy for confirmation of the diagnosis is imperative. At times, the tissue may have been removed from above or below the involved segment. Thus a negative biopsy report may be misleading.

The following gives the localization of the involved segment, and incidence of frequency: lower rectum, 38 per cent; lower and upper rectum, 48 per cent; rectosigmoid, 12 per cent; rectosigmoid alone or lower rectum and rectosigmoid, 2 per cent.

The characteristic clinical finding in this type of megacolon is stubborn constipation, yielding only to violent laxation. This is followed by copious evacuation of fetid fecal material. There is abdominal distention, quite prominent in the upper epigastric region, disturbance of the general state of health of the patient, and retarded growth. While this syndrome is ordinarily noted in older children, it may be observed in infants as early as nine months.

In the authors' series of 12 cases, 9 patients fitted into the above picture. There were 5 infants between the ages of four and eleven months and there were 4 children four, nine, fourteen and sixteen years of age, respectively.

The authors stress the importance of roentgenologic studies in determining the localization as well as the extent of colonic involvement. The plain roentgenogram may reveal massive dilatation with fluid levels in the upright position which may be erroneously interpreted as evidence of obstruction. Barium studies more dramatically show the extent of dilatation of any given segment of the colon as well as the point of differentiation between the involved segment and the normal.—*William H. Shehadi, M.D.*

HILLEMANT, P., MIALARET, J., and BOUTELIER, D. (Paris, France.) Exclusion duodénale et ostéomalacie des gastrectomisés. (Duodenal exexclusion and osteomalacia in gastrectomized patients.) *Presse méd.*, Mar. 22, 1961, 69, 627-630.

Contrary to the commonly held opinion, the authors think that osteomalacia is a frequent sequel to gastrectomy, especially in female patients, and its severity is in direct proportion to the duration of surgical exclusion of the duodenum.

A sixty-five year old female was hospitalized for steatorrhea, osteoarticular pains, marked loss of

weight and tenacious osteomalacia developed during a nine year period after subtotal gastrectomy (two-thirds of the stomach had been resected with exclusion of the duodenum). Surgical re-establishment of the duodenal circuit (the afferent jejunal loop was anastomosed to the second portion of the duodenum, thus establishing a gastrojejuno-duodenojejunal conduit) was effective in bringing about clinical recovery (except for steatorrhea) in nine months and healing of the osteomalacia in twenty-two months. This healing was remarkable in that all other therapeutic measures applied before had failed. No calcium therapy was instituted after the surgical re-establishment of the duodenal circuit, and this in spite of the persistence of steatorrhea. Hence, the authors point out the importance of the duodenum for the absorption and utilization of calcium.

A review of various theories as to the pathogenesis of osteomalacia after gastrectomy is presented and the prime importance of exclusion of the duodenal circuit is stressed.—*Jirair N. Sarian, M.D.*

NORMAN, ALEX, and SAGHATOLESLAMI, MEHDI.

Oral extrahepatic cholangiography: a simple reliable technic. *Radiology*, May, 1961, 76, 801-804. (Address: A. Norman, Hospital for Joint Diseases, 1919 Madison Ave., New York 35, N. Y.)

The purpose of this paper is to present a technique of "complete" oral cholecystography that will visualize the entire biliary system with the aid of a synthetic chologogue and no adjuvant drugs. The method of the examination is reviewed, stressing the importance of the right posterior oblique view in the determination of contractility, with the roentgenogram taken ten minutes following the fat meal as being the most significant for "complete" oral cholecystocholangiography. Anatomically and physiologically the right posterior oblique view of the gallbladder is more correct since the cystic and common ducts assume a more dependent position in relation to the gallbladder allowing for better diffusion of the heavier bile-contrast medium toward the neck of the gallbladder and into the extrahepatic ducts, facilitating the escape of gas from the more dependent right colon toward the splenic flexure or distal colon and anatomically affording better exposure of the extrahepatic duct system.

The importance of "complete oral cholecystocholangiography" in localizing calculi in the extrahepatic ducts is apparent. Of equal value are: determination of anomalies of insertion of the cystic duct; localization of obstruction in the biliary duct; evaluation of disease of the head of the pancreas; and lastly the defining of lesions about the ampulla and second part of the duodenum. By the technique described, extrahepatic duct visualization was obtained in 85 per cent of 100 examinations.—*Walter H. Jarvis, Jr., M.D.*

KAPLAN, ALLAN A., TRAITZ, JAMES J., MITCHEL, STANLEY D., and BLOCK, ALVIN L. Percutaneous transhepatic cholangiography. *Ann. Int. Med.*, 1961, 54, 856-869. (Address: A. A. Kaplan, 1674 Meridian Ave., Miami Beach 39, Fla.)

The merits of this procedure which, with relative safety and accuracy, differentiates between hepatocellular jaundice and obstructive jaundice are discussed and the technique is explained in some detail. The indications are listed and the list is expanded to include elucidation of the structure of the biliary tree in cases of suspected congenital biliary atresia. The cholangiogram in such patients may demonstrate the lesion, and, further, indicate whether the proximal biliary radicles are of a caliber to permit corrective surgical anastomosis with the gut.

In preparation, after evaluation of the coagulation mechanism, the fasting patient is premedicated and the injection site just below the midcostal margin is infiltrated with 2 per cent xylocaine through all layers into the liver capsule. A six inch 18 gauge spinal needle with stylet is introduced into the liver to a depth of four inches at an angle of 45° cephalad in the sagittal plane. The stylet is removed and plastic tubing connects the needle and a syringe. Gentle suction is applied to the syringe and the needle is slowly withdrawn during normal respiratory pauses until bile is aspirated. As much bile as possible is removed and 25 ml. of 70 per cent urokon sodium is introduced into the bile radicle. Cholangiograms are obtained and, finally, as much of the opaque medium and bile as possible is again aspirated to decompress the system. At this point, if desired, a No. 50 plastic catheter can be introduced into the biliary tree for further decompression. The aspirated bile may be cultured and examined histologically. If a vessel is entered, the needle is partially withdrawn and the system flushed. When, after four attempts, a biliary radicle is not entered a liver biopsy is done immediately without fear of creating bile peritonitis since it may be assumed that no dilated biliary radicles are present.

The procedure was employed 40 times and the biliary tree demonstrated in 30 of these patients. Of the 10 patients whose biliary system was not opacified, 8 had hepatocellular jaundice. The 2 "diagnostic failures" were eventually shown to have disease due to obstruction, but the accuracy of the procedure is of the highest order.

There was no mortality due to the procedure. Eight patients noted moderate pain after needle withdrawal. However, 4 developed signs of marked bile peritonitis and were immediately operated upon. All of these showed localized chemical peritonitis. There were no hemorrhagic complications. It is emphasized that immediate surgery should be available, if needed.

The procedure, as planned, provides either a

graphic demonstration of biliary obstruction or a tissue diagnosis of hepatocellular disease. In the interest of safety the importance of decompression of the biliary tree is stressed. Puncture is contraindicated in the presence of a significantly impaired coagulation mechanism. The use of flexible plastic tubing in the system makes hepatic laceration unlikely.

It is interesting to note that patients with severe pruritus obtained almost immediate relief with decompression of the biliary tree.

Six illustrative case histories with reproductions of roentgenograms conclude the paper.—*Jack Reynolds, M.D.*

LEGER, LUCIEN. Images de dilatation du canal de Wirsung; essai de classification. (Visualization of dilatation of the canal of Wirsung; an attempt at classification.) *Presse méd.*, Mar. 22, 1961, 69, 631-633. (From: Clinique chirurgicale de l'Hôpital Cochin, Paris, France.)

At present, three combined surgical and roentgenographic methods for exploration of the pancreas are possible: (1) transpancreatic puncture of the duct of Wirsung, (2) descending pancreatography following section of the pancreas, and (3) catheterization through the ampulla of Vater. The author has been able to catheterize without section of the sphincter of Oddi, which is less traumatic than catheterization after section of the sphincter. Catheterization is a so an effective therapeutic measure for drainage of the pancreatic secretion. Transpancreatic puncture of the duct of Wirsung, when possible, gives the most complete and clear roentgenographic visualization of the duct and canaliculi of the pancreas.

The canal of Wirsung is not always uniformly dilated; hence, the author attempts the following classification: (1) total dilatation of the canal of Wirsung and its principal tributaries; (2) dilatation of the cephalic part of the pancreatic duct which may be cylindrical or globular in form, the latter simulating a pseudocyst; (3) bipolar dilatation of the pancreatic duct (most probably due to narrowing of the pancreatic duct in the isthmus portion, which would also explain the prevalence of pancreatic calculi in this region); (4) dilatation of the canal of Wirsung at the body and caudal portions of the pancreas; and (5) pseudocysts of the pancreatic duct, which most probably are sequelae of necrotic foci within the pancreas and which are usually small and discrete and can be demonstrated only by pancreatography.

The author has not been able to correlate these dilatations chronologically or logically as to sequence. However, determination of the type of surgical treatment is influenced by these roentgen findings of different dilatations.—*Jirair N. Sarian, M.D.*

MICHEL, J. (Tours, France.) Étude radiologique de la mucoviscidose du pancréas. (Radio-

logic study of mucoviscidosis of the pancreas.) *J. de radiol., d'électrol. et de méd. nucléaire*, Mar.-Apr., 1961, 42, 114-121.

Mucoviscidosis of the pancreas (fibrocystic disease) has become a rather frequently diagnosed disease as a result of the works of Schwachmann in the United States and Lelong in France. During a period of five years the author studied 22 cases. All but 4 were examined roentgenologically. These 4 patients died soon after admission and the diagnosis was confirmed on autopsy.

The 18 patients who were observed for varying lengths of time presented the following striking findings: (1) frequent, though tardy appearance of digestive disturbances; (2) predominance and rather constant early respiratory difficulty; and (3) high susceptibility to infection.

The roentgenographic studies included routine posteroanterior and lateral films. Fluoroscopy, occasionally done, confirmed the roentgenographic findings. Laminagraphy was, at times, performed. Bronchography should, however, be discouraged. In one moribund patient, with bronchiectasis, bronchography precipitated acute respiratory insufficiency which finally improved under oxygen therapy.

The striking clinical signs and symptoms are respiratory distress appearing early within the first few weeks or months of life, at the latest, toward the end of the first year. Cough, dyspnea on effort, paroxysmal dyspnea, eventually continuous dyspnea and cyanosis occur; bronchopulmonary infection is frequent and is followed by bronchiectasis.

The roentgen findings include accentuation and thickening of the lung markings throughout both fields, segmental or lobar atelectasis, localized or diffuse pulmonary infiltration, prominence of the hilar shadows and eventually emphysema. Cor pulmonale develops with marked cardiac enlargement.

Sections of the lungs, after death, reveal obstruction of the bronchi by mucopurulent plugs and congestion of the bronchial mucosa.

While the pulmonary changes are the most striking roentgen findings, of considerable interest are changes in the abdomen which include meconium ileus and meconium peritonitis.

Of the 105 cases observed by Schwachmann through a seventeen year period, there were 10 deaths. Many, however, were not until a lapse of six to twelve years. Of 95 living children, 47 were improved as compared with their initial status, 27 remained stationary and 21 were worse. Forty-one lived beyond ten years and 1 lived beyond twenty-two years. Ten had meconium ileus which was surgically treated.

While the disease is recognized to be quite serious, these statistics indicate that the patient may live for many years. This thesis has been stressed by American workers and in a large measure is contrary to the general thinking of French students of this subject.—*William H. Shehadi, M.D.*

GYNECOLOGY AND OBSTETRICS

HEAGY, FRED C., and SWARTZ, DONALD P. Localizing the placenta with radioactive iodinated human serum albumin. *Radiology*, June, 1961, 76, 936-944. (Address: F. C. Heagy, 346 South Street, London, Ont., Canada.)

Localization of the placenta is important in the management of the obstetric patient with third trimester antepartum bleeding. After excluding other causes of bleeding, the authors studied 42 patients to attempt localization of the placenta, and especially to rule out placenta previa. The method used was to inject 3 μ c of radioactive iodinated human serum albumin into the antecubital vein, and fifteen minutes later determine the activity rates over the abdomen using the precordium as a standard. The thyroid was blocked by using Lugol's solution for 48 hours previously, or for 2 weeks afterward. Counting rates were done with a scintillation counter at a right angle to the skin, and in a horizontal position laterally.

In 15 of the 42 patients placenta previa was suspected, and isotopic examination suggested that 2 of them might have placenta previa. Both of these were confirmed as having partial placenta previa. In 5 of the patients studied the fetus had died *in utero*. In 2 of these there was no area of increased activity, but in 3 there was, suggesting a functioning placenta. The observation that the placenta may continue to function after fetal death is relevant to the theory of afibrinogenemia production in cases of retained dead infants.

It is stressed that the pattern of counts is the most important factor in attempting localization of the placenta. A uniformly low count suggests a midline posterior location, or else nonfunction. The amount of radiation to the mother is estimated to total less than 100 millirads, and less than 4 millirads to the infant. If Lugol's solution is used, there should be no localization of I^{131} in the thyroid after the albumen breaks down, and there is of course no localization at once as the I^{131} is attached to the albumen and stays in the maternal blood pool.—*J. C. Moore, M.D.*

HAMILL, GEORGE C., JARMAN, JULIAN A., and WYNNE, MORGAN D. Fetal effects of radioactive iodine therapy in a pregnant woman with thyroid cancer. *Am. J. Obst. & Gynec.*, June, 1961, 81, 1018-1023. (From: Radioisotope Section and Thyroid Clinic, Maxwell, Ala.)

Radioiodine therapy in millicurie dose ranges may be used in selected cases to inactivate functioning metastasis. This report may serve two functions; *i.e.*, to show possible injurious effects of I^{131} on a fetus, and to illustrate eradication of functional cervical metastasis, follicular type, with systemic radiotherapy employing I^{131} .

A woman with functioning thyroïdal cervical metastasis was treated with 77 mc of I^{131} when three months pregnant. A chemical protein bound iodine determination in the child at eight days of age established the presence of circulating thyroid hormone. The baby was born prematurely, weighing four and one-half pounds. During the first two months after birth, no evidence of cretinism was present, but hypothyroidism subsequently developed and the child was placed on oral thyroid extract at eighty-three days of age. The child had been well and had been maintained on oral thyroid extract for twenty months but then developed repeated convulsions which are at present under good control with appropriate medication. The dose received by the fetal thyroid may have been very great or very small. Ascertainment of the pregnancy status in all women prior to I^{131} is suggested.—*Eugene J. McDonald, M.D.*

LEWIS, R. H. Foetus in foetu and the retroperitoneal teratoma. *Arch. Dis. Childhood*, May, 1961, 36, 220-226. (From: Llandough Hospital, United Cardiff Hospitals, Cardiff, Wales.)

Foetus in foetu, a descriptive term attributed to Meckel, should be applied only to those rare cases where a parasitic twin is found included within the abdomen of its partner. Lord (1954; 1956) reported 2 definite cases and reviewed other possible cases.

In contrast, the variety of teratoma which occurs in the retroperitoneal space is much less defined. Many theories of origin have been suggested, with some authors contending that the teratoma represents a form of included twin. Although this is now unacceptable, it has resulted in the description of many retroperitoneal teratomas in confusing terms.

Willis (1958) pointed out the separate nature of the retroperitoneal teratoma and foetus in foetu, emphasizing that the former is a true tumor while the latter is not. However, as both conditions occur in the upper part of the retroperitoneal space, it is not surprising that terms such as "foetus in foetu," "parasitic twin," and "suppressed twin" have been misapplied to teratomas having a marked degree of differentiation and some foetiform characteristic.

The purpose of this report is (1) to describe a further case where borderline pathologic features are present; (2) to discuss and compare briefly the pathology of foetus in foetu and retroperitoneal teratoma; and (3) to discuss their symptoms, physical signs, diagnosis and treatment.

Symptoms and signs are due to the pressure effects of the tumor, and while initially vague, become increasingly persistent as the tumor enlarges. This is especially so in the case of retroperitoneal teratoma where pressure effects tend to be more severe.

Treatment is by surgical removal of the tumor without undue delay. Depending on the age and condition of the patient and the anatomic relations of

the tumor, it may be considered advisable to remove the foetus only from within its sac.

The potentially malignant nature of the teratoma, and of other similarly situated tumors when the diagnosis is doubtful, calls for early operation.—*Eugene J. McDonald, M.D.*

WELLS, JOSEPHINE, and STEER, CHARLES M. Relationship of leukemia in children to abdominal irradiation of mothers during pregnancy. *Am. J. Obst. & Gynec.*, June, 1961, 87, 1059-1063. (From: Department of Radiology and Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University and the Radiological and Obstetrical and Gynecological Services of the Presbyterian Hospital in the City of New York, New York, N. Y.)

The frequency of roentgen examination of the abdomen during pregnancy in the mothers of a group of children who died of leukemia is compared with the frequency of such examination in the mothers of a control group of children.

Among 77 mothers of children who died of leukemia, prenatal abdominal roentgen examination was carried out in 4, an incidence of 5.2 per cent. Among the 156 controls, abdominal roentgen examination was carried out in 11, an incidence of 7.1 per cent.

These figures neither prove nor disprove a relation between roentgenographic examination of the abdomen during pregnancy and the subsequent development of leukemia in the child.

It is concluded that roentgen examination should continue to be performed during pregnancy in those cases in which clinical examination determines the need for it.—*Eugene J. McDonald, M.D.*

GENTOURINARY SYSTEM

TRUC, E., BÉTOULIÈRES, P., PALEIRAC, R., and HENRIET, R. (Montpellier, France.) L'examen radiologique dans les traumatismes du rein. (Radiologic examination in traumas of kidney.) *J. de radiol., d'électrol. et de méd. nucléaire*, Mar.-Apr., 1961, 42, 93-100.

The value of roentgenologic examination of the urinary tract following injury to the thoracolumbar area is stressed by the authors. Their studies are based on 20 patients.

The examination may be performed by the following methods:

(1) The *plain film method*. This may reveal alterations in size and contour of the affected kidney or total loss of its shadow. It may also reveal changes in the adjacent bone structures, such as fracture of the ribs, vertebral bodies or their processes. There may

be accompanying distention of the intestines, due to ileus masking the urinary tract and adjacent bone structures.

(2) *Intravenous urography*. This is the most important single roentgenologic examination. It may be performed immediately, within the first forty-eight hours, or as soon as the patient has recovered from shock. It may be repeated at intervals to determine the progress and changes which develop in renal function. Intravenous urography may reveal total loss of renal function, decreased renal function as evidenced by delayed or decreased excretion, or at times normal function. The value of delayed urograms, particularly where initial renal function is absent or decreased, cannot be overemphasized. By means of excretion urography the function, but not the morphology, of the kidney is estimated.

In one-third of the patients examined there was one-sided total loss of the renal function, immediately following trauma, with return to normal in two weeks to six months. In 4 patients there was renal atrophy with progressive decrease in the size of the renal shadow and extent of the renal excretion. There was permanent, total loss of function in 1 case. Marked hydronephrosis, dilatation of one renal pelvis with stenosis at the pyelocalyceal junction and subcapsular extravasation of the contrast medium was noted, respectively, in 3 different patients.

(3) *Retrograde urography*. This should be done with caution. The chief indication is total loss of function as evidenced by intravenous urography, where, based on clinical observation, surgical intervention is imperative. The chief advantage of this examination is that it delineates the anatomic status of the parts involved. It supplements but does not replace intravenous urography. In case of absence of renal function it is the only way in which the status of the ureter may be determined.

(4) *Retroperitoneal insufflation*. Its indications are limited. It may be helpful in evaluating the extent of perirenal changes following hematoma or infection.

There was total return of renal function to normal in 12 cases, while permanent damage persisted in the other 8 cases.—*William H. Shehadi, M.D.*

HINMAN, FRANK, JR. Peripelvic extravasation during intravenous urography, evidence for an additional route for backflow after ureteral obstruction. *J. Urol.*, Mar., 1961, 85, 385-397. (Address: 801 Heyburn Building, Louisville, Ky.)

In 5 patients with ureteral obstruction, the author has noted extravasation of urine about the renal pelvis and upper ureter during intravenous pyelography. Experimental observations on adult and infant kidneys obtained at autopsy showed that contrast material injected under pressure permeated the connective tissue separating the calyx from the renal pa-

renchyma and was distributed around the renal papilla in the fornix.

This is interpreted as evidence of a potential route for the spread of substances from the pelvis to the peripelvic region. The peripelvic connective tissue is relatively loose and infiltrated with fat which permits an anatomic route between the rim of the calyx and the renal hilus.

Such extravasations are seen in retrograde pyelography and also occasionally in the obstructed ureter after intravenous injection of contrast medium for excretory pyelography. Observations indicate that intrapelvic pressures are reduced during the time of backflow. Once a backflow has been established, less pressure is required to maintain it and the increased tone of the renal pelvis probably plays a role in extravasation, since pelvic dilatation is absent or reduced in such instances. It is assumed that, in those patients who show a nephrogram as a result of ureteral obstruction, an adequate route for backflow has not been established and the contrast medium remains in the renal tubules. Passage of a ureteral catheter in such a case produces an immediate pyelogram because it releases the intrapelvic pressure and allows the medium in the tubules to pass into the renal pelvis. In other instances in which fairly clear pyelograms are seen but no backflow can be detected, in spite of ureteral obstruction, the urine probably passes into the lymphatic or venous circulation and is not visualized on the roentgenogram. The appearance of extravasated medium during intravenous urography in the presence of ureteral obstruction from calculi occurs quickly, while extravasation from abdominal compression of the lower ureters occurs over a somewhat longer period of time.

Fibrosis in the peripelvic and periureteral tissue could result from single or repeated urinary extravasation in the renal sinus. In some instances, a jelly-like material has been found in the retroperitoneal tissue which has been ascribed to the foreign body reaction to sterile urine. In other such instances, interstitial infiltration of perirenal tissues in cases of chronic urinary tract obstructions have been described. It is entirely possible that the end result of these processes is peripelvic and periureteral fibrosis.—*George W. Chamberlin, M.D.*

HARROW, BENEDICT R., and SLOANE, JACK A. Pyelorenal extravasation during excretory urography. *J. Urol.*, June, 1961, 85, 995-1005. (Address: B. R. Harrow, 2621 Biscayne Boulevard, Miami 37, Fla.)

The use of the more radiopaque contrast media and ureteral compression for excretory pyelography has resulted in a number of observations of extravasation of opaque medium from the renal pelvis.

The authors describe in detail a case of pyelosinus extravasation seen on intravenous urograms due to backflow of the medium in the renal sinus which sup-

posedly was initiated by prolonged compression over the ureters. Arciform shadows, presumed to be due to arcuate vein infiltration, were shown to be in reality perivascular extensions of the pyelosinus backflow. In this instance, the diagnosis of renal neoplasm was at first entertained but urograms obtained six months later were normal.

Extensive pyelosinus extravasation occurred spontaneously during excretory urography in 2 patients during episodes of renal colic. In these patients, the medium spread in the renal sinus and in the perirenal fat outside the renal capsule. Pyelosinus backflow, with extension in arciform shadows adjacent to the calyces and occasional extension into the lymphatics, can be produced by prolonged compression during intravenous urography in a significant number of cases. Actual pyelovenous reflux has rarely been shown at either excretory or retrograde pyelography, although it undoubtedly occurs occasionally during the latter.—*George W. Chamberlin, M.D.*

MONACO, HORACIO, O'CONNOR, TOMAS EDUARDO, and MOUREU, RICARDO SANCHEZ. Desembocadura ureterovulvar en una malformación pieloureteral doble. (An ectopic ureterovulvar opening in a double ureter malformation.) *Prensa méd. argent.*, Oct. 28, 1960, 47, 2924-2927. (Address: H. Monaco, Mansilla 2440, Buenos Aires, Argentina.)

A case is presented of a congenital anomaly of the right kidney pelvis and ureter with an ectopic opening. The patient was a thirty-four year old female complaining of mild incontinence since childhood. On physical examination the authors observed an opening in the vulva which appeared to be excreting clear fluid. Intravenous and retrograde pyelograms revealed the presence of a single ureter and pelvis on the right. The pelvis was smaller than normal indicating that it corresponded only to the lower pole of the right kidney. There was also a double ureter on the left but with a normal single opening into the urinary bladder.

A tentative diagnosis of a double ureter on the right with an ectopic opening into the vulva was made and confirmed at laparotomy. The ectopic (medial) ureter was observed to be dilated and a transplant of the ureter into the bladder was performed.

The patient's postoperative course was uneventful. The authors point out that catheterization of the ectopic opening is usually diagnostic but sometimes difficult or impossible to perform.—*Cesar E. Rosa Perez, M.D.*

PORIES, WALTER J., McDONALD, DONALD F., and HINSHAW, J. RAYMOND. A calibrated radiopaque Penrose drain. *J. Urol.*, Mar., 1961, 85, 405-407. (From: Department of

Surgery and Division of Urology, University of Rochester School of Medicine, Rochester 20, N. Y.)

The authors point out the advantages of a Penrose drain which is radiopaque in order that it may be located when lost in the soft tissues and also calibrated so that its length may be checked as it is advanced from the wound.

These drains have a characteristic red color and are impregnated with barium sulphate and cadmium solenide. They were tested for tissue reaction by implanting them in the subcutaneous tissues of animals, with minimal tissue reaction resulting. The radiopacity and the centimeter graduations were well maintained even after thirty-five days of implantation.

Radiopaque drains have been used in more than 100 patients during the past nine months without any unfavorable reactions. Multiple illustrations show the radiopaque nature and the photographic appearance of these drains.—George W. Chamberlin, M.D.

GIoustREMES, VASSILIOS, BOYARSKY, SAUL, and NEWMAN; HARRY R. Fatal air embolism following presacral air insufflation; occurrence despite manometric control. *J. Urol.*, Mar., 1961, 85, 381-384. (From: Division of Urology, Department of Surgery, Albert Einstein College of Medicine and Bronx Municipal Hospital Center, Bronx 61, N. Y.)

This is a case report of a sixty-four year old male patient who, after receiving 1,100 cc. of air injected under manometric control by the presacral route to the retroperitoneal area, went into coma, followed by cardiac standstill and, in spite of all attempts at resuscitation, died.

Autopsy revealed air bubbles mixed with blood of the pulmonary vessels in the lung. The right ventricle was filled with foamy blood. No air was seen in the coronary vessels. There was a large renal carcinoma involving the left kidney and it is theorized that the large vessels over this tumor could have been the site of entrance of the air into the circulation.

Experimentally, the authors found that, in the presence of obstruction to the egress of air from the second bottle, air is compressed until the flow of water from the first bottle is topped. At this point, release of resistance allowed a sudden rush of most of the air contained in the second bottle. At pressures of 100 cm. of water, the volume released was 135 cc. Retroperitoneal pressures had been found to be 10-15 cm. of water and venous pressure is rarely over 20 cm. of water. Thus, in the presence of a high degree of resistance in the retroperitoneal soft tissues and sudden release, the two-bottle manometric method of injection of air may cause as rapid an injection of

air as the syringe method. Unless the pressure in the system is adjusted low enough so that any trapping of air is prevented, manometric control is actually a misnomer. Should the gas enter the circulation, the rate of entry and the volume and solubility of the gas determine the outcome. Because of its high solubility, carbon dioxide is the only gas which the body can remove rapidly enough under all conditions to prevent serious embolic phenomena. Massive doses of carbon dioxide, in animals and patients, have been shown to be safe.

A review of the literature has shown that 58 fatal reactions and 68 near fatal reactions have been reported in the experience of 1,267 urologists. The incidence of severe reactions with oxygen is the same as with air. It is suggested that presacral injection of air should not be done in the presence of acute infections, large renal or retroperitoneal tumors, or fascial plane malignancies. Carbon dioxide should be used in preference to oxygen, air, or helium.—George W. Chamberlin, M.D.

SCHMIDLAPP, CARL J., II. Respiratory (cardiac) arrest after retrograde pyelography with neomycin-containing medium. *J. Urol.*, June, 1961, 85, 993-994. (Address: 99 Forest Avenue, Glen Cove, N. Y.)

The author reports in detail an instance of respiratory arrest following the use of 3 cc. of retrografen for pyelography. The total amount of neomycin in the retrografen was estimated as 50 to 70 mg. The patient was under general anesthesia with ether oxygen mixture. Sixty minutes after the retrograde injection of the radiopaque medium containing neomycin, apnea occurred with muscle flaccidity. No pulse, blood pressure, or heart beat was obtainable. Closed chest resuscitation was carried out for two minutes without benefit and then a thoracotomy was done. Cardiac massage was carried out, the pericardium was opened, and 5 cc. of 20 per cent calcium gluconate was injected into the left ventricle. The heart beat immediately improved, respirations were resumed, and the blood vessels in the wound began to bleed. The chest was closed and the postoperative course was uneventful.

It has been shown experimentally that neomycin can cause neuromuscular blockade with a curare-like action and its effect is potentiated by ether anesthesia. This curare-like action is antagonized by calcium and neostigmine. Increasing numbers of instances of respiratory arrest following the use of intraperitoneally administered neomycin have been reported, usually occurring within twenty minutes after the injection.

The series of events occurring in this case is similar to that in other cases of reported respiratory arrest occurring after peritoneal absorption of neomycin into the circulation. Rapid reversal of the process by the intraventricular injection of calcium also paral-

lels the clinical and experimental reports.—George W. Chamberlin, M.D.

FELTON, LESTER M. Should intravenous pyelography be a routine procedure for children with cryptorchism and hypospadias? *J. Urol.*, Feb., 1959, 81, 335-338. (From: Department of Surgery (Urology), James Buchanan Brady Foundation of The New York Hospital and Cornell University Medical College, New York, N. Y.)

In an attempt to evaluate the radiation hazards versus the useful and positive findings in the urinary tract of children with cryptorchism and hypospadias, the author has reviewed this subject with the following findings.

In a series of 289 boys under the age of fourteen admitted to the hospital for cryptorchism, 61 underwent intravenous pyelography. Of the 61, 13.5 per cent showed major abnormalities and 6.5 per cent showed minor abnormalities of the urinary tract.

Of 142 boys who had hypospadias, 36 per cent had intravenous pyelography performed and, of these, 9 per cent showed major abnormalities of the urinary tract.

The cause of death was evaluated in 169 consecutive autopsies performed on boys between the ages of two and fourteen years. The author found that tumors and abnormalities of the urinary tract and the juxtarenal area accounted for 17 deaths in this group. In comparing these statistics, it is noted that, of the male patients with cryptorchism, 13.5 per cent had unsuspected urinary tract abnormalities, whereas in the routine autopsy series only 2.1 per cent had unsuspected urinary tract disease.

The author summarizes these findings and indicates that a properly performed roentgen examination, using the minimum number of exposures necessary and shielding the gonads to the best of the radiologist's ability, is a proper and justified procedure in the routine examination of patients with cryptorchism. In the group with hypospadias, there is less justification for routine intravenous pyelography. In most instances where both cryptorchism and hypospadias are present pyelography should be done.—George W. Chamberlin, M.D.

STEVENSON, J., MACGREGOR, A. M., and CONNELLY, P. Calcification of the adrenal glands in young children; a report of three cases with a review of the literature. *Arch. Dis. Childhood*, 1961, 36, 316-320. (From: University Department of Infectious Diseases, Ruchill Hospital, Glasgow, Scotland.)

The authors present 3 cases of bilateral adrenal calcification in infants (aged seven weeks, one and one-half years, and two years) which was incidentally found during care for other clinical conditions. None

of these cases showed clinical evidence of decreased adrenal function and have continued in good health after recovery from the primary illness cared for. A slight degree of extension in the calcification was noted in the seven week old infant on serial roentgenograms.

A general discussion of the causes of adrenal calcification is presented. The most frequent cause is thought to be hemorrhage at or about the time of birth. Prematurity, difficult deliveries and asphyxia seem to predispose to hemorrhage.

Adrenal calcifications are usually found incidentally and are of little clinical importance. In some, definite signs and symptoms may be present in the form of increased response to infection or stress, focal or generalized epileptiform seizures produced by hypoglycemia, and as classic Addison's disease with pigmentation.—George A. Miller, M.D.

NERVOUS SYSTEM

SVIEN, HENDRIK J., and BAKER, HILLIER L., JR. Roentgenographic and surgical aspects of vascular anomalies of the spinal cord. *Surg., Gynec. & Obst.*, 1961, 112, 729-735. (From: Sections of Neurologic Surgery and Roentgenology, Mayo Clinic, and the Mayo Foundation, Rochester, Minn.)

The authors have reviewed 32 cases of such lesions. They frequently cause alterations in the dynamics of the cerebral spinal fluid in its total protein and cellular content but measurement of these abnormalities may not suggest the proper diagnosis. Roentgenographic examinations are the only diagnostic procedures by which the character and extent of a lesion may be determined accurately prior to its exposure at operation. Rarely do routine roentgenograms of the spine yield helpful information but positive contrast myelography is usually diagnostic. They prefer to use 9 to 12 ml. of pantopaque injected by lumbar puncture with the patient in the prone position; often it is found useful to employ the oblique and supine positions as well, to outline the subarachnoid space more completely.

Characteristically the vessels which comprise the vascular anomaly are visualized as negative shadows varying between 1 to 4 mm. in width, easily distinguishable from the normal spinal arteries. Sometimes these abnormal vessels are shown to involve the entire length of the spinal canal but in other cases more localized involvement is present. Occasionally a complete block to the flow of contrast medium is encountered and sometimes vigorous pulsation of the abnormal vessels permits recognition of the arteriovenous character of the anomaly. Adhesive arachnoiditis and spinal cord tumors are usually easily differentiated.

The authors have been unable to demonstrate upper cervical lesions by angiography. Transosseous

venography outlines so many venous channels in thoracic lesions that it is impossible to distinguish the abnormal from the normal vessels and consequently this method of examination has not proven helpful. Cineradiography may record pulsations of the vessels not ordinarily visible by fluoroscopy.

The authors' experience with surgery in these cases parallels that in the majority of reports of relatively large series of cases. Decompression has very little to offer and both excision and ligation are fraught with dangers of cutting off the blood supply to other parts of the cord and of producing thrombosis in the intramedullary vessels and aggravating symptoms. However, surgery is justified: (1) when there is persistent, intractable pain; (2) when there is progressive neurologic loss with manometric and myelographic indication of subarachnoid block; and (3) when diagnosis of intramedullary hematoma is made.—*A. E. Childe, M.D.*

CURTISS, PAUL H., JR., and COLLINS, WILLIAM F. Spinal-cord tumor—a cause of progressive neurological changes in children with scoliosis; a report of three cases. *J. Bone & Joint Surg.*, 1961, 43-A, 517-522. (From: Divisions of Orthopaedic Surgery and Neurosurgery, Department of Surgery, Western Reserve University School of Medicine, Cleveland, Ohio.)

With neurologic disorders of the cord there may be a progressive scoliosis as seen in developmental defects of the nervous system, Friedreich's ataxia, von Recklinghausen's neurofibromatosis, syringomyelia or poliomyelitis.

In previously reported cases of established scoliosis which later developed paraplegia the etiology has included unequal growth of the dura and spinal column, sudden increase in scoliosis, tight dural band, spur of bone, angulation of the cord or tightness of the nerve roots.

Spinal cord tumor must also be considered and 3 cases of intradural astrocytoma are presented. In each case there had been a diagnosis of poliomyelitis in childhood, followed by scoliosis and then progressive neurologic changes. Roentgenograms in 2 cases showed relatively slight scoliosis and interpeduncular widening was not demonstrated. Myelograms in all cases revealed complete block.

Intradural tumors should be suspected when there is a history of early transient neurologic deficit with later development of scoliosis and eventual progressive paresis thought due to mechanical cord compression.—*Martha Mottram, M.D.*

BLIGH, A. S. Diastematomyelia. *Clin. Radiol.*, July, 1961, 12, 158-163. (From: Department of Radiology, Cardiff Royal Infirmary, Cardiff, England.)

Diastematomyelia is defined as a congenital mal-

formation of the neural axis, characterized by a sagittal division of the spinal cord or cauda equina. Separating these two parts of the cord there may be an osseous, cartilaginous or fibrocartilaginous septum which is attached anteriorly to the body of one or more vertebrae, and either free posteriorly or attached to a neural arch. The commonest site of the lesion is in the dorsolumbar area, but it may occur elsewhere in the vertebral column. Over 100 cases have been reported in the literature. The author uses 11 additional cases to illustrate the main roentgenologic features.

There may be multiple congenital anomalies, such as block vertebra, missing pedicles and neural arch defects. The interpedicular distances are increased but there is usually no flattening or erosion of the pedicles,—this suggesting the congenital nature of the lesion. The spur or septum may be seen in the anteroposterior projection, but only if sufficient calcium is present to produce the necessary roentgenographic density.

Myelography will confirm the presence of a central spur or septum, appearing as a negative shadow within the opaque medium column. Myelography is also of value in the demonstration of two meningeal tubes when present.

The author urges the necessity of considering the possibility of diastematomyelia wherever gross spinal anomalies are seen, especially in the dorsolumbar area, and in the roentgen examination of a young child. The condition can produce severe disability but if diagnosed early enough surgery offers much relief.—*Samuel G. Henderson, M.D.*

SKELETAL SYSTEM

VAN CANEGHEM, PIERRE, and SCHIRREN, CARL GEORG. Über den Einfluss der verwendeten Strahlenqualität auf das Ausmass von Knochenwachstumsschädigungen bei Bestrahlungen von Kückenbeinen im Tarso-Metatarsal-Gelenk. (The influence of radiation quality on inhibition of growth by irradiation of the tarso-metatarsal joints of chicks.) *Strahlentherapie*, Mar., 1961, 114, 370-375. (From: Dermatologische Klinik und Poliklinik der Universität, München, Germany.)

Irradiation of the tarso-metatarsal region of 48-hour old chicks showed that growth inhibition is independent of the quality of the radiation in the half-value layer range from 1.8 mm. Al to 4 mm. Cu, and that gamma rays of radium inhibit growth to the same degree as roentgen rays.—*Henry G. Moehring, M.D.*

HAYES, JOHN T. Cystic tuberculosis of the proximal tibial metaphysis with associated involvement of the epiphysis and epiphyseal

plate; a report of two cases. *J. Bone & Joint Surg.*, 1961, 43-A, 560-567. (From: Department of Surgery, Section of Orthopaedic Surgery, University of Michigan, Ann Arbor, Mich.)

Two cases of cystic tuberculosis involving the proximal tibial metaphysis, epiphyseal plate and epiphysis are reported in children aged two and six.

In one case, the initial symptom was a painful knee and in the other a fluctuant mass in the left gastrocnemius extending up to the popliteal space. In spite of specific drug therapy and immobilization the lesions progressed; therefore, curettage was done. Pus giving positive cultures for tuberculosis, considerable granulation tissue and small sequestra were obtained.

Roentgenograms of both patients showed lytic areas in the tibial epiphysis and metaphysis which enlarged but did not involve the knee joint or erode the superior articular cortex. In the younger patient there was erosion of the posterior tibial cortex and abscess formation in the soft tissues.

The patients have had no growth disturbance in three and five and one-half years follow-up and symmetric tibial growth has continued.—*Martha Mottram, M.D.*

BEZES, H. Lesions osseuses des mycetomes du pied. (Osseous lesions of mycetoma of the foot) *Presse méd.*, Mar. 25, 1961, 69, 1-4. (From: Service de Clinique chirurgicale de la Faculté de Médecine de Dakar, Sénégal.)

Mycetoma is the most common fungus infection involving bony structures. Between 1956 and 1959, of 50 cases of mycetoma of the foot which were examined by the author, 29 showed osseous involvement (about 58 per cent).

All of the bones of the foot can be invaded by all colors of granules of this fungus. However, the scaphoid, cuboid, cuneiform and metatarsal bones are the more susceptible ones. The roentgenographic findings are quite typical, even sometimes to the point of being diagnostic as to the color of granule of the fungus invading the bones. However, there are cases where the osseous involvement is discrete and not characteristic.

In general, a double process is involved. A destructive and osteoporotic or osteolytic process is followed by reactionary healing or a condensing process with osteoperiostitis. Osteolytic processes can be noted in various forms, such as a honeycomb appearance of the bones, cyst formations of various sizes, foci of cortical destruction, moth-eaten appearance of the bones, and partial to complete dissolution or destruction of bones without any sequestration. The healing or reactionary process will cause condensation of the bone and periosteal thickening, which at times may simulate a sarcomatous lesion. The metatarsals and

the phalanges may become filiform and undulated and, at times, extraordinary synostoses between the tarsal, metatarsal and phalangeal bones can be noted.

The author feels that further study would be necessary to be able to correlate the roentgenographic findings to the color of the granules of the invading fungus.—*Jirair N. Sarian, M.D.*

VARADARAJAN, M. G. Actinomycosis of bone. *Punjab M. J.*, 1961, 10, 321-324. (From: Madras Medical College and Government General Hospital, Madras, India.)

Bone involvement in actinomycosis is usually the result of direct extension from a primary infection of the soft parts. The author reports such a case. The patient gave a history of the disease beginning with a pustular lesion in the soft tissues of the left forearm; by a process of healing and extension the whole of the forearm, elbow, and lower half of the upper arm had been covered with multiple pustular lesions in various stages of healing and activity. Examination showed multiple sinuses exuding a pus-like secretion. There was also diffuse swelling of the whole upper extremity.

Roentgenograms revealed multiple circumscribed areas of reduced density in the humerus, radius, and ulna due to bone destruction. There was also sclerosis of bone representing reaction to the infection, but the destructive process was more marked than the new bone formation.—*Douglas S. Kellogg, M.D.*

MACKENZIE, ALAN, COURT BROWN, W. M., DOLL, R., and SISSONS, H. A. Mortality from primary tumours of bone in England and Wales. *Brit. M. J.*, 1961, 2, 1782-1790. (Address: W. M. Court Brown, Medical Research Council's Clinical Effects of Radiation Research Unit, Western General Hospital, Edinburgh, Scotland.)

The authors have investigated the mortality attributed to primary malignant tumors of bone during 1951-53 in persons under 65 years of age. They estimate that 597 deaths from primary bone tumors occurred in persons under 65 years of age in England and Wales during these three years with a minimal annual mortality of 6.3 per million in men and 3.9 per million in women.

The greatest mortality from tumors of the limb bones occurred in both sexes at ages of 15 to 19 years and at this age the ratio of the male to the female was at its maximum (2.1 to 1). The mortality from such tumors fell from the age of 20 to 34 years and then rose again from the age of 40 years. This increase over the age of 40 years was largely due to tumors associated with Paget's disease. The mortality from tumors of the limb bones not associated with Paget's disease increased slowly between the ages of 35 and 64 years and was equal in both sexes.

At the ages of 45 years and over there was a sharp increase in the mortality among men but very little increase among women. In the absence of Paget's disease, the discrepancy was more marked. The male excess in this group was due principally to tumors of the ribs and shoulder girdle.

The authors have been unable to find any significance in geographic distribution of bone tumor mortality in England and Wales.—*A. E. Childe, M.D.*

PHALEN, GEORGE S., and DICKSON, JAMES A. Spondylolisthesis and tight hamstrings. *J. Bone & Joint Surg.*, 1961, 43-A, 505-512. (From: Department of Orthopedic Surgery, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute, Cleveland, Ohio.)

The association of tight hamstrings with spondylolisthesis is uncommon. Tightness, spasm or contraction of the hamstring muscles often accompanies tumors of, or tumors that compress, the cauda equina; a contracted filum terminale; diastematomyelia; large protruded disks; trauma; inflammatory lesions or advanced spondylolisthesis.

Two cases are reported with well-marked spondylolistheses, Grade III and IV of the 5th lumbar vertebra on the sacrum. Both patients walked with a peculiar gait and had markedly limited forward flexion when standing. Straight leg raising was limited but unassociated with pain. There was severe spasm and tightness of the hamstrings, which kept the pelvis and trunk tilted backwards.

Surgery showed an extremely taut sciatic nerve in one patient and stretched first sacral nerve roots in the other. The first patient had reoperation and the cauda equina was tightly stretched over the body of S1. Following decompression, both children have walked normally. Local measures to stretch or lengthen the hamstrings are not of value.—*Martha Mottram, M.D.*

CHILDE, ARTHUR E., and TUCKER, F. R. Spondylarthritis in infants and children. *J. Canad. A. Radiologists*, 1961, 12, 47-51. (From: The Children's Hospital, Winnipeg, Manitoba, Canada.)

Spondylarthritis is presumably an inflammatory process of the intervertebral disk occurring in infants and young children. No organism has ever been isolated. There are four main types of syndromes: (1) meningeal, (2) back pain, (3) abdominal pain, and (4) hip joint pain. The onset is fairly abrupt with low-grade fever, mild leukocytosis, and increase in sedimentation rate. Regardless of the type of therapy, the patients improve quite rapidly with complete clinical recovery.

The roentgenographic changes are narrowing of the disk space with roughening and absorption of the

margins of the adjacent vertebral bodies. This usually occurs in the low thoracic or lumbar region. Even after complete clinical recovery, disk narrowing with marginal sclerosis usually persists and, in some cases, there is bony fusion between the two involved vertebral bodies.

This disease can usually be differentiated from Pott's disease by a negative tuberculin test in a child who is not very ill. True osteomyelitis may also be excluded by the clinical course.—*W. C. MacCarty, Jr., M.D.*

VESPIGNANI, L., and ZORAT, G. Diagnosi artrografica del menisco discoidale (4 casi). (Arthrographic diagnosis of discoid meniscus [4 cases].) *Radiol. med.*, Mar., 1961, 47, 208-218. (Address: L. Vespignani, Reparto Radiologico, Ospedale Civile, Mirano, Venezia, Italy.)

The discoid meniscus is a rare congenital anomaly in which the meniscus instead of having the normal semilunar form, is abnormally wide and presents the appearance of a more or less complete disc. The malformation affects the lateral meniscus more frequently.

The discoid meniscus is subject to more frequent rupture and cystic degeneration.

The conventional roentgenologic examination of the knee does not provide conclusive criteria.

The authors have used the Lindblom technique routinely, i.e. arthrography with a water soluble opaque contrast medium. They consider the method eminently satisfactory both because it is innocuous and precise diagnostically.—*A. A. Blasi, M.D.*

BLOOD AND LYMPH SYSTEM

ROY, PAUL, JUTRAS, ALBERT, and LONGTIN, MARCEL. Extra large field angiography: technique and results. *J. Canad. A. Radiologists*, 1961, 12, 27-35. (From: Department of Radiology, Hôtel Dieu de Montréal, Montréal, Québec, Canada.)

Ever since abdominal aortography and femoral arteriography were inaugurated, there has been a definite need for very large serial roentgenograms that would cover, in a single exposure, the whole abdomen and the lower extremities. The authors describe an apparatus designed by them which accomplishes these results.

The reasons for the success obtained with this device are the following: (1) Simultaneous visualization of the entire arterial system of the abdomen and lower legs; (2) uniform roentgenographic density with very good detail and contrast; (3) minimum radiation exposure to the patient; (4) complete radiation safety for the personnel; (5) accurate timing and film exposure; and (6) easy handling and smooth performance of the examination.

In the preliminary planning of experimentation, the following elements were taken into account:

1. The focus film distance in relation to the length and width of the anatomic surface to be covered, which was finally established at 76 inches from the table top.
2. Optimum use of the dispersion properties of the anode in accordance with the notion which is referred to as the "heel effect." The abdomen should be placed under the cathode side and the feet, which require less radiation, directed toward the anode side.
3. Construction of a special cone adapted to the required shape of the roentgen-ray beam. The walls of this cone were sheathed with lead to cut off unwanted radiation and it was made asymmetric with a more abrupt slope cephalad than caudad.
4. Proper selection of antidiffusion grids. For the abdominal part, a 10:1 ratio grid was adopted. For the thighs, the ratio was reduced to 8:1. No. grid is employed for the legs and the feet where tissue volume is smaller.
5. Adjustment of film sensitivity to thickness of anatomic parts. After repeated trials, the empirical formula agreed upon is as follows: (a) abdominal region: high speed screen film for stout patients, medium speed screen film for slender subjects; (b) femoral region: medium speed screen film for all patients; and (c) legs and feet: no screen film.
6. Choice and position of intensifying screens. For the abdomen two high speed screens are used. For the femoral area only one medium speed screen is required. The film of the distal extremities is exposed without any screen at all.
7. Construction of the 3-step filter. The filter is made of a very resistant aluminum alloy. It consists of three wedged parts, the thickest portions having a greater absorption power in the caudal direction. The filter is installed in a slit through the lead slab at the tube end of the localizing cone. Actually, the filter is the key element in the system. In its final state, the filter proved satisfactory after exacting an almost microscopic work.
8. Cassettes of nonstandard dimensions. A special cassette was designed measuring 51 inches by 14 inches in which could be inserted three 17×14 inch roentgenographic films in an end-to-end arrangement.
9. Automatic cassette changer. A series of four superimposed drawers were designed to carry the special cassettes described above. The bottoms of these drawers are lined with a layer of lead $\frac{1}{4}$ of an inch thick. These drawers move on rails. Before examination they are all brought under the table where the patient lies. They are held in place by means of electromagnets. After each exposure, drawers are automatically released and pushed out of the way by weight traction and stored under a large lead panel. The lowest drawer is located 9 inches from the table top. The very long tube film distance (76 inches) and

the accurately collimated roentgen-ray beam eliminate distortion. The lowermost films and those from the top cassettes can be matched perfectly.

10. Empirical establishment and subsequent codification of roentgenographic factors. The authors have a technique chart which adapts readily to their requirements. Films are exposed at 2.5 seconds, 7 seconds, 15 seconds, and 25 seconds after the beginning of the injection. Injection time is 2.5 seconds.

11. Radiation dose received by the patients, absorption of the rays in tissues and their scattering in the neighborhood of a table. The skin dose was found to be between 440 and 550 mr, measured in the pubic region, depending upon the thickness of the patient. These figures compare favorably with the mean roentgen-ray dose resulting from barium enema examination or even intravenous urography.

A fifteen month test of this equipment proved the unequivocal diagnostic efficiency and technical feasibility of these extra large field serial angiographies. The equipment is certainly very ingenious and the reader interested in using it is referred to the original article.—*W. C. MacCarty, Jr., M.D.*

PEDRO-BOTET, J. Utilidad diagnóstica de la esplenoportografía en el síndrome de Cruveilhier-Baumgarten. (Diagnostic use of splenoportography in the Cruveilhier-Baumgarten syndrome.) *An. med.*, Oct., 1960, 46, 419-425.

The Cruveilhier-Baumgarten syndrome is usually diagnosed clinically by the existence of visible venous varicosities in the periumbilical area, "caput medusae." This finding indicates an abundant collateral circulation through the umbilical and periumbilical veins in cases of portal hypertension.

The author reports a series of 98 splenoportographies of which 4 revealed the presence of the Cruveilhier-Baumgarten syndrome. Two of the cases were clinically diagnosed prior to the splenoportography. The other 2 were not diagnosed clinically, since there were no visible veins, and the diagnosis was established by splenoportography alone.

The author emphasizes the importance of splenoportography prior to any surgical intervention for portal hypertension since, in his series, 50 per cent of the cases of this condition were diagnosed only after this examination was performed.

The four cases of the Cruveilhier-Baumgarten syndrome are presented with reproductions of the splenoportograms and diagrammatic illustrations of the roentgen findings.—*Cesar E. Rosa Perez, M.D.*

PIPER, D. W. A radiographic study of the portal and hepatic venous systems in cirrhosis of the liver. *Am. J. Digest. Dis.*, 1961, 6, 499-510. (From: Department of Medicine, University of Sydney and Unit of Clinical In-

vestigation, Royal North Shore Hospital of Sydney, Sydney, Australia.)

The vascular abnormalities present in cirrhosis are somewhat controversial as are the causes of some of the clinical findings. The author studied 12 cirrhotic livers (etiology: 7, alcohol; 2, unknown; 2, hepatitis; and 1, hemochromatosis) and 6 normal livers by postmortem roentgenograms following injection of the hepatic and portal venous systems with bismuth oxyiodide.

Eleven cases showed an abnormal hepatic venous system consisting mainly of distortion of the small veins and difficult filling of the hepatic venous system. Irregular caliber of the veins was present in some instances. The portal venous system was apparently normal in all cases.

In this limited series, there was no correlation between the extent of vascular changes and the etiology of the cirrhosis or the clinical and laboratory findings present before death.—George A. Miller, M.D.

ASSCHER, A. W., WILSON, C., and ANSON, SALLY G. Sensitisation of blood-vessels to hypertensive damage by x-irradiation. *Lancet*, Mar. 18, 1961, 1, 580-583. (From: The Medical Unit, The London Hospital, E.1, London, England.)

The authors studied the effects of irradiation and hypertension separately and together on a loop of rat mesentery to determine whether roentgen irradiation increased the sensitivity of mesenteric arteries to hypertension.

They delivered 1,200 r to a marked, exteriorized loop of mesentery in each of 50 normotensive female rats and then restored the loop to the peritoneal cavity. They removed the left kidney and clipped the right renal artery at varying intervals ranging, from zero to four months after irradiation. The rats were killed one month after the renal artery was clipped.

The control groups consisted of: (1) 12 rats with irradiated loops whose renal arteries were not clipped and whose mesenteries were examined two months after irradiation; and (2) 6 groups of 10 rats each which received doses to the mesentery ranging from 200 to 1,200 r and whose renal arteries were clipped one month later.

Sensitisation of the mesenteric vessels to the damaging effect of hypertension was not evident until two months after irradiation with 1,200 r, and it continued for at least five months. The irradiated vessels appeared as thick cords with nodules palpable along their length in the animals which developed hypertension. In this study enough time had not elapsed for the blood pressure to reach the high levels required to produce vascular lesions in the nonirradiated parts of the mesentery or in the other tissues. Irradiation alone did not produce these

lesions; the irradiated controls which did not have the right renal artery clipped did not have any lesions. The controls which received less than 1,000 r did not develop arterial lesions, even after four months.

The authors conclude that two months after irradiation with 1,000 or 1,200 r the arterial wall becomes more vulnerable to the damaging effects of increased intravascular pressure.

The results of these experiments imply that, whatever the underlying mechanism, irradiation and raised intravascular pressure seem to be complementary in their damaging effects on the arterial walls. This theory may be relevant to the delayed tissue necrosis which occasionally follows therapeutic irradiation, and which is well known to be associated with arterial necrosis. We might expect the delayed tissue necrosis to arise with greater ease and frequency in hypertensive patients.—R. J. Noveroske, M.D.

GARCIA, NICHOLAS A., III, NELSON, JAMES H., JR., BERNSTINE, RICHARD L., HUSTON, J. WILSON, and GARTENLAUB, CHARLES. Findings on retrograde femoral arteriography in choriocarcinoma. *Am. J. Obst. & Gynec.*, Apr., 1961, 81, 706-710. (From: The Departments of Obstetrics and Gynecology and Radiology of the United States Naval Hospital, St. Albans, N. Y.)

The authors present a case demonstrating the occurrence of arteriovenous fistulas in a patient with histologically proved choriocarcinoma. The fistulas were observed roentgenologically within the area of a palpable pelvic mass. It was possible to demonstrate by arteriography the regression of the mass in response to amethopterin therapy. The changes in arteriographic findings were reflected by changes in the findings at pelvic examination as well as by the serum chorionic gonadotropin titers.

It is suggested that retrograde femoral arteriography may prove useful in the diagnosis of trophoblastic tumors where the wall of the uterus is involved deep to the endometrium.—Charles H. Helmen, M.D.

JACKSON, LAIRD, WALLACE, SIDNEY, SCHAFFER, BURTON, GOULD, JOHN, KRAMER, SIMON, and WEISS, ARTHUR J. The diagnostic value of lymphangiography. *Ann. Int. Med.*, 1961, 54, 870-882. (Address: A. J. Weiss, Associate in Medicine, Jefferson Medical College of Philadelphia, 1025 Walnut St., Philadelphia 7, Pa.)

The roentgenographic demonstration of the lymphatic system by intralymphatic injection of contrast material proves valuable not only diagnostically, but as a guide to therapeutics. By refined

technique, the authors are able to opacify the retroperitoneal lymph nodes and to delineate their architecture with a clarity which permits some precision in the diagnosis of abnormalities.

The method is briefly discussed and those interested are referred to publications which describe the technique in greater detail. Attention is directed to the appearance of the lymphangiogram in the normal and the abnormal, signs helpful in differentiating various diseased states and to the practical application of the knowledge gained.

When bilateral injection is made in the foot with the oily contrast medium containing 37 per cent iodine, the lymphatics and lymph nodes of the leg, inguinal, external and common iliac, paraortic and thoracic duct region and supraclavicular area are visualized. Injection of lymphatics of the hand opacifies the lymphatics of the arm, axillary and supraclavicular areas. The lymphatic ducts remain visualized for less than an hour in the normal. The lymph node architecture is best studied at twenty-four hours. Normal lymphatics are of fine caliber and course parallel to the veins. In lymphedema, hypoplasia of lymphatics may occur; occasionally there is dilatation and dermal backflow (filling of skin lymphatics). The normal lymph node appears globular or kidney-shaped and is about 1.5 cm in size, sometimes umbilicated at the hilus. There are several afferent vessels and fewer efferent. The internal structure is that of an even reticular pattern.

The appearance in the diseased state differs as to etiology: (1) In acute inflammation there is an increase in the number and size of visualized lymph nodes but they retain a normal peripheral contour and architecture. (2) Metastatic carcinoma produces an increase in the number and size of visualized lymph nodes and there are irregular filling defects at the margin of the lymph node giving a "moth eaten" appearance. Occasionally carcinoma may replace a lymph node and only the deviated lymphatic vessels reveal its presence. (3) Lymphoma produces large lymph nodes with a foamy or lacy pattern with preservation of the smooth outer margin. Within the lymphoma group there is a variation which permits more refined diagnosis: (a) lymphosarcoma appears as a prototype, (b) Hodgkin's disease is similar with the addition of scattered, punched-out areas of lucency in the center, (c) chronic lymphatic leukemia shows the basic pattern but with areas of increased opacity.

Several case reports make clear not only the diagnostic value of the procedure but its importance as a guide in treatment. Lymphangiography permits more exact localization of tumor site and delineates unexpected extension of malignancy depicting abnormal lymph nodes which may not be palpable. If injection is made prior to cancer surgery, a film exposed before closure may demonstrate remaining metastatic sites. It permits the evaluation of chemotherapy and allows periodic reevaluation in the

asymptomatic patient. Any modality which delineates retroperitoneal structures eases the problem of diagnosis of carcinoma of the pancreas and the authors allude to tentative signs which may aid in this difficult problem.

The procedure has been assayed in 140 patients and no serious complications have resulted. The venous system may be entered as it was in 6 patients with resultant fever, cough and mild dyspnea due to pulmonary embolization. The symptoms were of brief duration.—*Jack Reynolds, M.D.*

GENERAL

MORGAN, RUSSELL H. The measurement of radiant energy levels in diagnostic roentgenology. *Radiology*, June, 1961, 76, 867-876. (Address: Department of Radiology, The Johns Hopkins Hospital, Baltimore 5, Md.)

The biologic effects of repeated small doses of ionizing radiation have been the subject of considerable study in recent years. Irradiation of the reproductive system may cause mutations in succeeding generations, and irradiation of the hematopoietic system may lead to leukemia. Other biologic effects are known to occur as a result of chronic irradiation exposure but most of the current knowledge is more qualitative than quantitative. It is thought that through epidemiologic investigation it will be possible to gain considerable understanding, both qualitative and quantitative, of the effects of chronic radiation exposure if a sufficiently large number of individuals, subjected during their normal lives to small doses of irradiation, exhibits well defined biologic changes. There are now, within the United States, many people who receive these small doses of radiation in the course of their medical care who would be suitable for this epidemiologic research. Those who receive no radiation could be the control group. For this type of research it would be necessary to know the quantities of radiation these people had received. They would have to be followed for a sufficiently long period of time to detect any biologic changes which may occur. Important data would include: (1) the total energy contained within the roentgen-ray beams of the equipment used in practice; (2) the relationship between radiant energy values and tissue dose for the various types of roentgenographic and fluoroscopic examinations and for the various tissues.

The author describes in detail an instrument developed in his laboratory which permits the measurement of the total energy contained within a roentgen-ray beam. It is a device which integrates radiant energy both temporally and spatially. Measurements are made without the operator being required to determine the area of the irradiated field or the exposure time. Also, as its response is uniform at all photon energies, measurements may

be made without correction for kilovoltage and beam filtration. Normal operation, thus, is quite simple, and requires no adjustments or manipulation except for the simple pushing of a reset switch at the end of each exposure, after the measurement has been recorded, in order to prepare it for the next exposure. Although designed principally for epidemiologic research, this ease of use makes it ideal for the routine recording of radiation exposure data in diagnostic roentgenology. It is calibrated to give readings in absolute units of radiant energy; namely, the millijoule.

This routine recording of the radiant energy delivered to patients is likely to have an important influence on roentgenographic and fluoroscopic techniques. High readings will point to unsafe equipment or improper fluoroscopic procedures. Awareness of these high exposures will lead to correction of defective equipment and the improvement of techniques, thus ensuring that the exposure received by the population from medical roentgenologic sources is maintained at as low a level as possible.—*Donald N. Dysart, M.D.*

RADIATION THERAPY

YANGUAS, MARIO GAITÁN. Tratamiento de la peritendinitis (bursitis) con rayos x; estudio de 285 casos. (Treatment of peritendinitis (bursitis) with roentgen rays; review of 285 cases.) *Radiología*, Mar., 1961, 11, 51-62. (Address: Director-Jefe de Radioterapia del Instituto Nacional de Cancerología de Bogotá, Carrera 12 No. 20-69, Bogotá, Colombia.)

The author reviews his experience in the treatment of 242 patients suffering from bursitis. A number of patients had bilateral lesions; thus, the total number of lesions is 285, with 94 per cent of them localized in the shoulder region, about equally divided between the right and left side. Only 16 per cent of the patients gave a history of previous trauma, and another 16 per cent showed evidence of rheumatic disease. Of the 260 cases with roentgen studies of the shoulder, 88 per cent had calcifications, but there seemed to be little correlation between the intensity and duration of symptoms and the presence of calcium deposits; moreover, the deposits would often persist after treatment had rendered the patient asymptomatic.

Irradiation was administered with roentgen rays of a half value layer of at least 1 mm. Cu, through 6×8 to 8×10 cm. fields, in divided doses from 100 to 300 r daily. The total dose was never higher than 2,000 r given over a period of several weeks.

In evaluating the results, 26 cases were eliminated from consideration because the patients had received no treatment or because the treatment was not completed. Of the remaining 259, 79 per cent had complete relief of symptoms, 6 per cent noticed no improvement, and the rest experienced partial benefit. Only 72 patients could be rechecked a year after treatment and 63 of them were well.—*F. Comas, M.D.*

PELÙ, G. Considerazioni sulla radioterapia del tumore di Wilms; con particolare riguardo ai risultati a lunga distanza dal trattamento della sede primitiva e delle metastasi. (Consideration of radiotherapy of Wilms' tumor; with particular attention to the long term results of treatment of the primary site and of the metastasis.) *Radiol med.*, Mar., 1961, 47, 229-241. (Address: Piazza della Vittoria, 10, Firenze, Italy.)

The patients observed, with the exception of one who because of bilateral lesions was treated palliatively by irradiation alone, were treated by a combination of surgery and irradiation.

The validity of the method is justified by the early extension of the neoplasm beyond the limits of the renal capsule, and the possibility of dissemination of neoplastic cells during the operative intervention.

A depth dose of 2,700-3,000 r was administered, whenever possible, immediately after nephrectomy.

Opposed anterior and posterior fields and occasionally, when necessary, a lateral field were used. The fields covered the superior limit of the hemidiaphragm and the contralateral side of the spine in order to include the vascular root and the lymphatic distribution.

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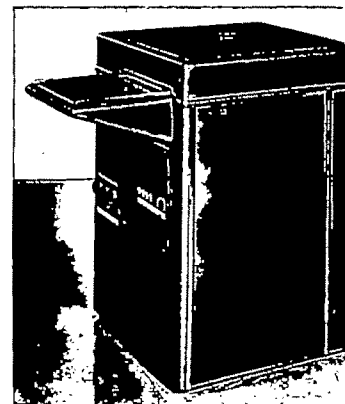
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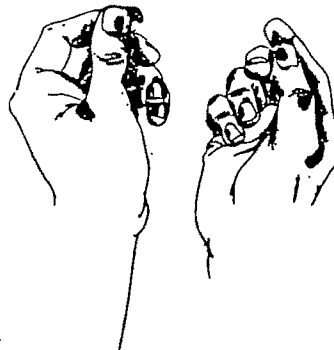
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Associated Electrical Industries Ltd.	xxxvi
Atomic Energy of Canada Limited	xxiii
Automatic Seriograph Corporation (Division of Litton Industries, Inc.)	1
Barnes-Hind Laboratories	Second cover
Bell-Craig, Inc.	xxvi
British Institute of Radiology	xlx
Buck X-Ograph Company	xlx
Charleston Rubber Company	viii
Du Pont de Nemours, E. I. & Co. (Inc.)	xxi, xxii
Eastman Kodak Company	xli, xlii
Fougera, E. & Company, Inc.	xiv, xv
General Electric Company	xxx, xxxi, xxxii, xxxiii, xxxiv, xxxv
Hunt, Philip A., Company	xxxvii
Ilford, Inc.	xxvii
Karger, S.	xliv
Liberty Protective Leathers, Inc.	xlvi
Liebel-Flarsheim Company (Division of Ritter Company, Inc.)	xviii
Low X-Ray Corporation	vi
McElroy, Donald, Inc.	xlvi
Nuclear-Chicago Corporation	ix, x, xi, xii
Ortho Pharmaceutical Corporation	vii
Pickering X-Ray Corporation	xiii, Fourth cover
Profexray, Inc.	i
Schick X-Ray Company	xxxix
Siemens-New York, Inc.	xx
Squibb, E. R. & Sons	v, xix, Third cover
Standard X-Ray Company	xxiv, xxv
Thomas, Charles C, Publisher	xxxviii, xlvi
Georg Thieme Verlag	xliii
Westinghouse Electric Company	xl
Winthrop Laboratories	xxviii, xxix

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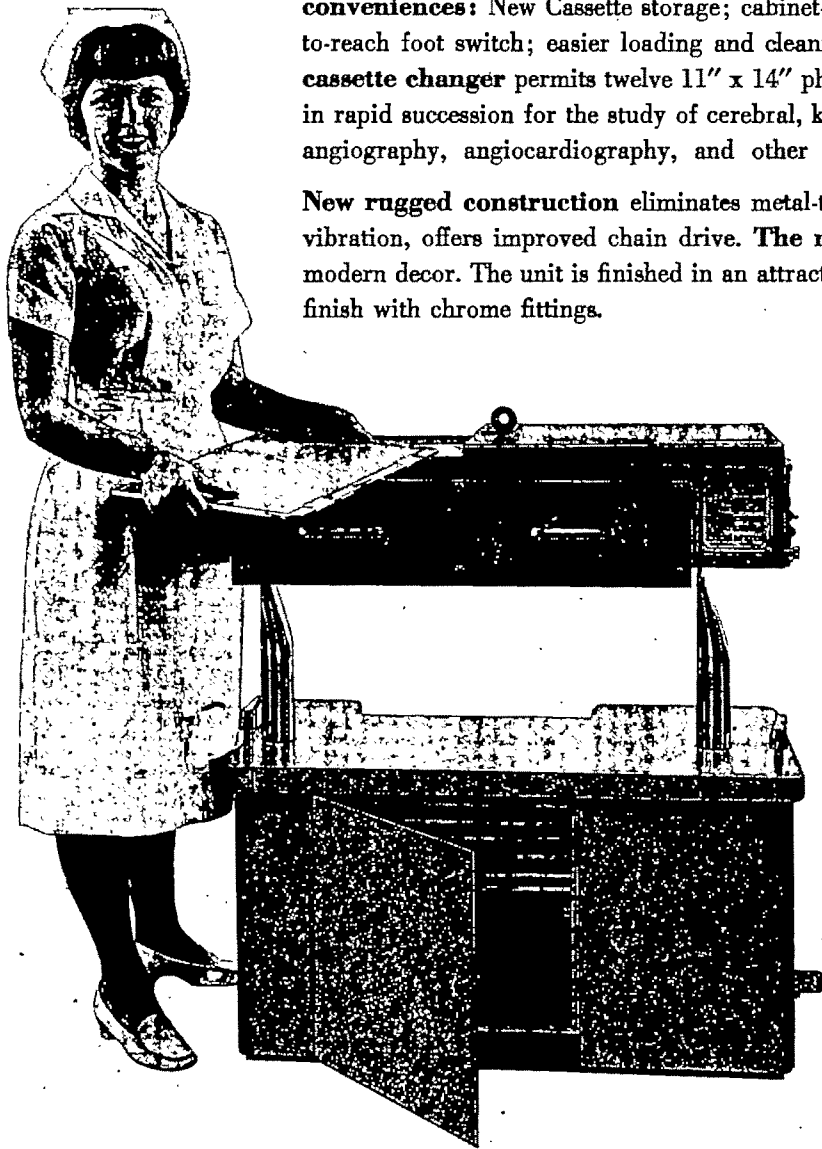
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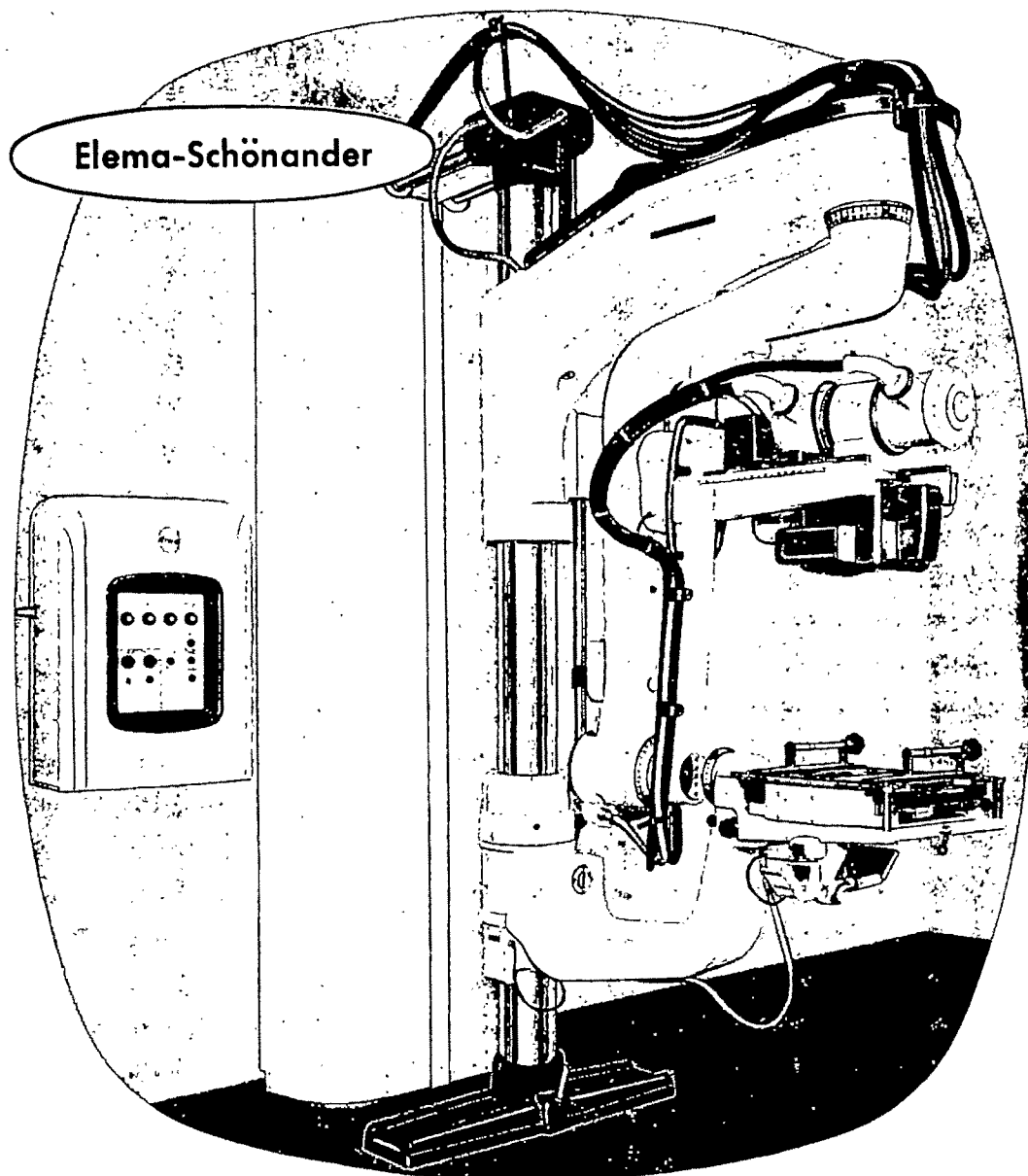
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CONTENTS

- The Azygos Vein Arch and Its Valvular Apparatus; Angiographic Observations.* GIULIO TORI, M.D., AND G. F. GARUSI, M.D. 235
- Dilatation of the Hemiazygos Veins in Superior Vena Caval Occlusion Simulating Mediastinal Tumor.* ISRAEL STEINBERG, M.D. 248
- Experimental Coronary Arteriography Using Roentgenographic Magnification.* TIMOTHY TAKARO, M.D., STEWART M. SCOTT, M.D., AND WILLIAM H. SEWELL, M.D. 258
- Percutaneous Arterial Catheterization and Its Application.* KURT AMPLATZ, M.D. 265
- The Use of Percutaneous Transfemoral Aortography to Diagnose Abnormalities of the Renal Arteries.* JAMES M. STOKES, M.D., AND ERIK CARLSSON, M.D. 276
- Hepatic Artery Aneurysm; Case Report.* JAMES L. QUINN, III, M.D., AND JAMES F. MARTIN, M.D. 284
- Uterine Arteriography in Hydatidiform Mole.* JAIME ROCA, RUBEN VILLAMAYOR, JOSÉ LLAURÓ, AND RAFAEL FLICHTENTREI. 287
- An Approach to Femoral Arteriography; A Long Film Changer.* FRED C. SHIPPS, M.D. 291
- The Jet Sign in the Angiocardiographic Diagnosis of Anomalous Pulmonary Venous Drainage.* ISRAEL STEINBERG, M.D., AND DANIEL S. LUKAS, M.D. 294
- Angiographic Patterns of Cerebral Convexity Veins and Superficial Dural Sinuses.* GIOVANNI DI CHIRO, M.D. 308
- The Posterior Inferior Cerebellar Artery on Vertebral Angiography.* BERNARD S. WOLF, M.D., CHARLES M. NEWMAN, M.D., AND MANSHO T. KHLNANI, M.D. 322

(Continued on p. iv)

<i>The Significance of Protein Binding of Contrast Media in Roentgen Diagnosis.</i> ELLIOTT C. LASSER, M.D., RICHARD S. FARR, M.D., TAK FUJIMAGARI, M.D., AND WALTER N. TRIPP, M.D.	338
<i>A Modified Lumbar Puncture Needle for Pneumoencephalography.</i> BERNARD S. EPSTEIN, M.D., AND JOSEPH A. EPSTEIN, M.D.. . . .	361
<i>Three Simple Devices to Facilitate Contrast Neuroroentgenography.</i> M. M. SCHECHTER, M.D., AND LAWRENCE STRENGER, M.D.	363
<i>An Autotomographic Appliance.</i> EDMUND H. BURROWS, M.B., CH.B., D.M.R.D.	366
<i>Primary Spinal Tumors: A Seven-Year Study.</i> ARTHUR S. TUCKER, M.D., BISAMAI ARAMSRI, M.D., AND W. JAMES GARDNER, M.D.	371
<i>Bronchogenic Carcinoma; A Comparative Study of the Palliative Effects of Ra- diation Therapy, Radiation Therapy Plus Nitrogen Mustard, and Radi- ation Therapy Plus Amethopterin and Actinomycin D in Combination.</i> LESLIE L. ALEXANDER, M.D., JULIA CAUSING, M.D., HAROLD N. SCHWINGER, M.D., AND MIN CHIU LI, M.D.	375
<i>Sialography of the Submaxillary Salivary Gland; A New Technique.</i> S. GORDON CASTIGLIANO, M.D., F.A.C.S.	385
<i>Detail Visibility in Radiographs: An Experimental and Theoretical Study of Geometric and Absorption Unsharpness.</i> K. ROSSMANN, PH.D.	387
<i>Duplication of Roentgenograms by Solarization.</i> JOSHUA A. BECKER, M.D., AND DEWEY P. BLACKSTONE, R.T.	394
<i>Officers</i>	397
<i>Editorial</i>	
<i>Radiation Registry of Physicians</i>	398
<i>News Items</i>	400
<i>Book Reviews</i>	403
<i>Books Received</i>	404
<i>Abstracts of Radiological Literature</i>	405

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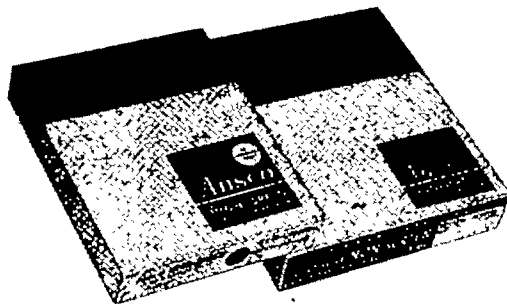
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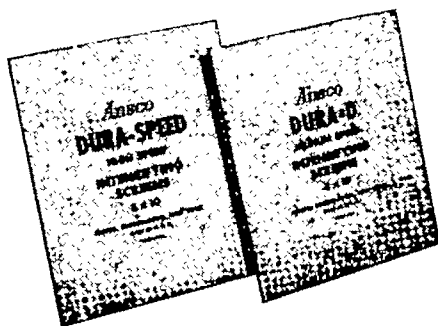
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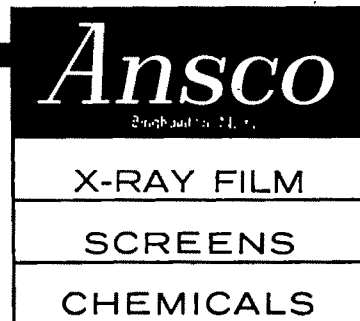
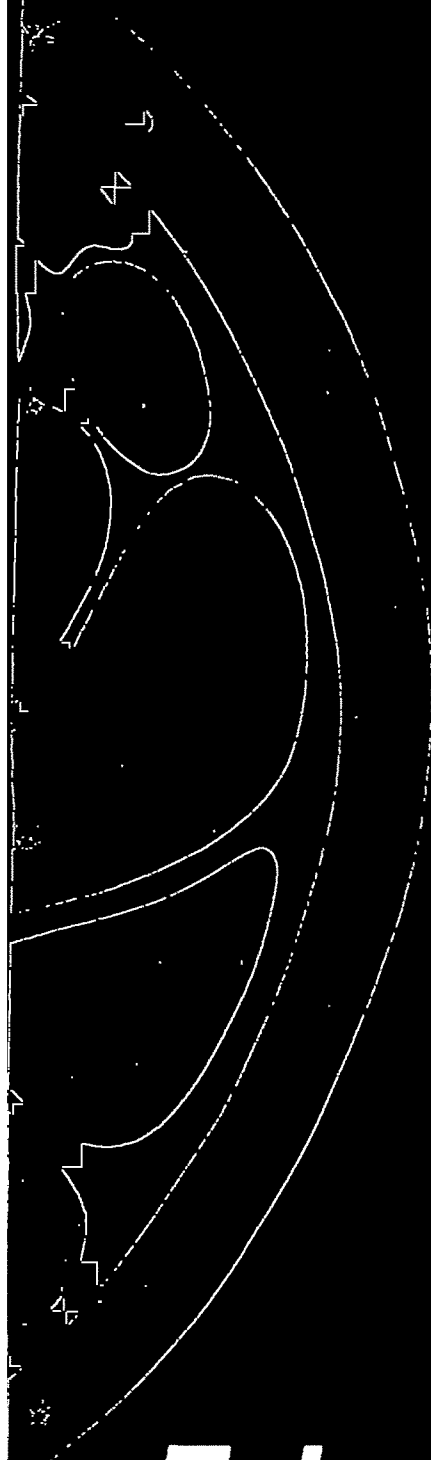




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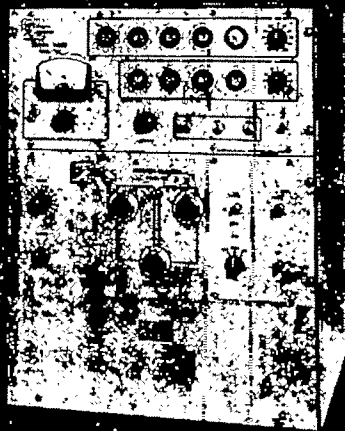
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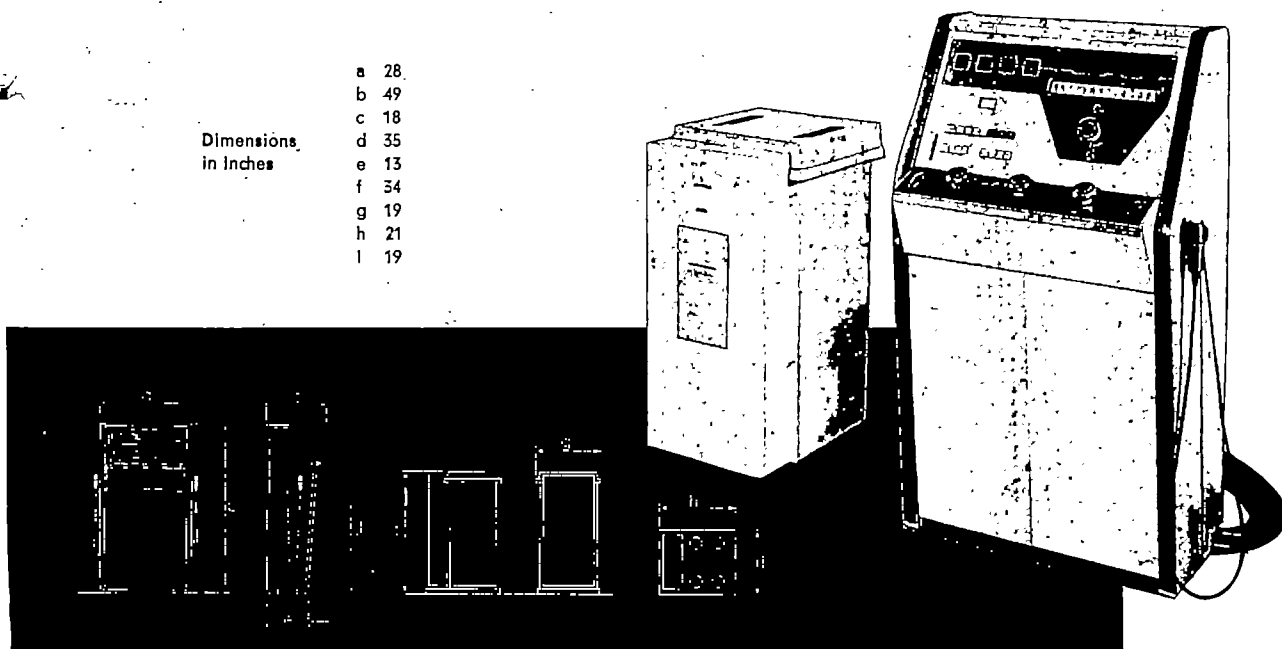
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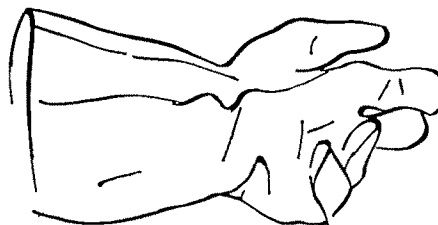
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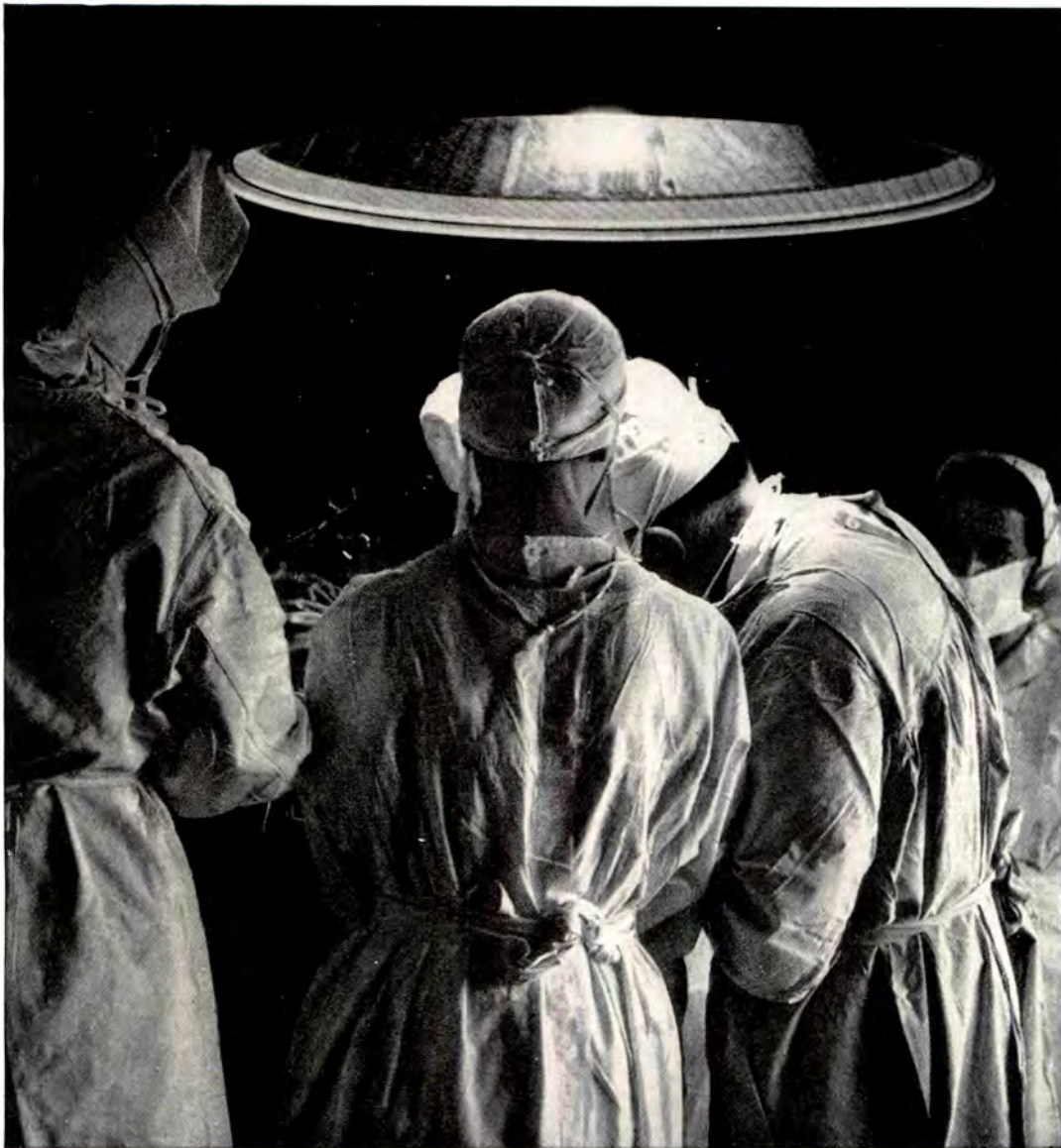


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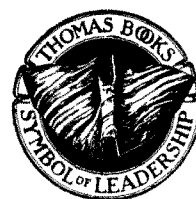
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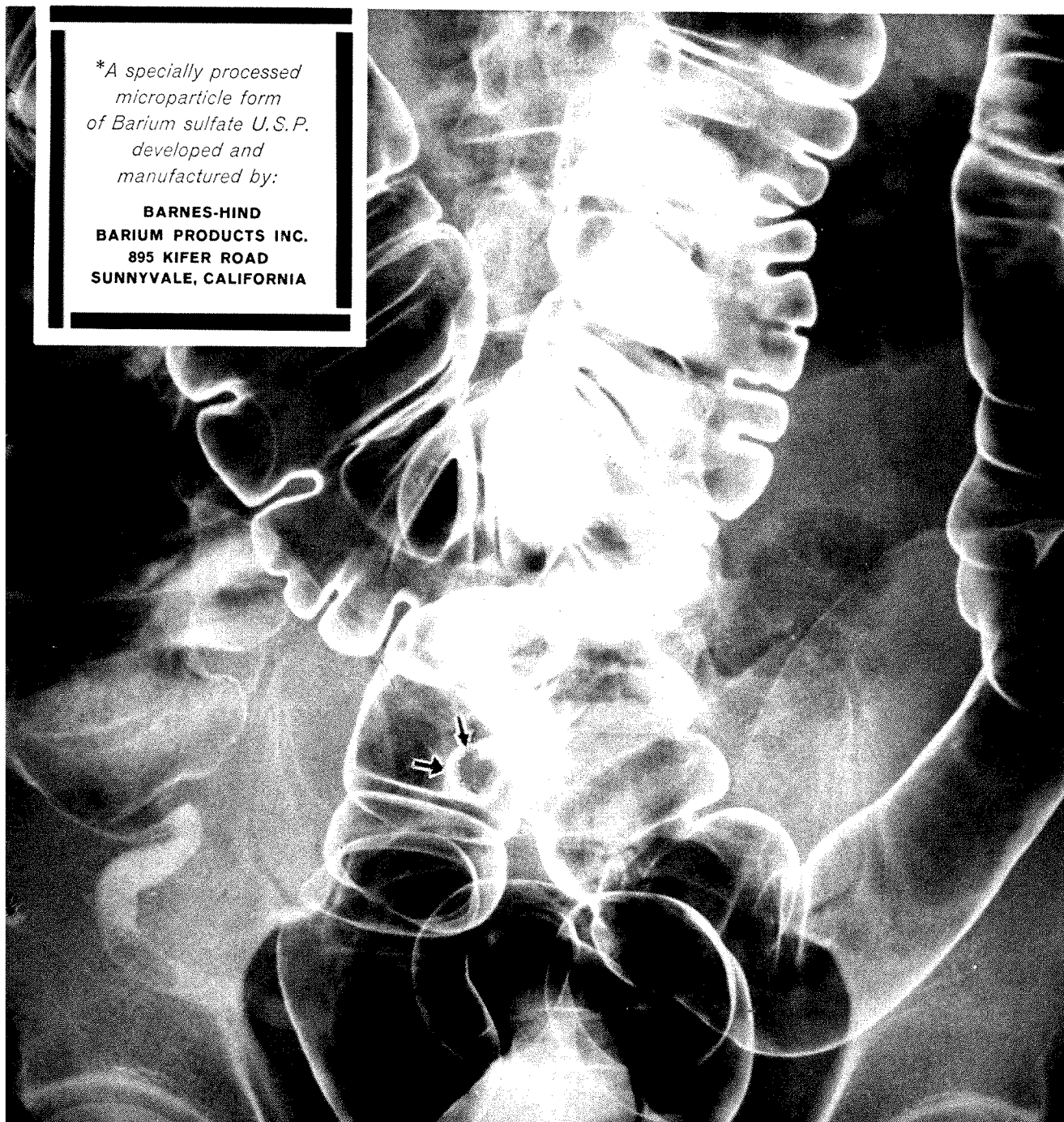
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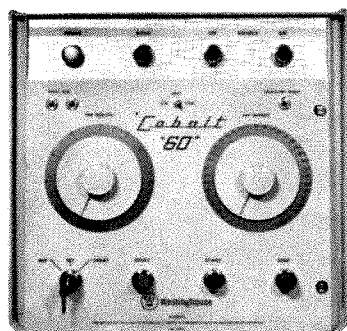
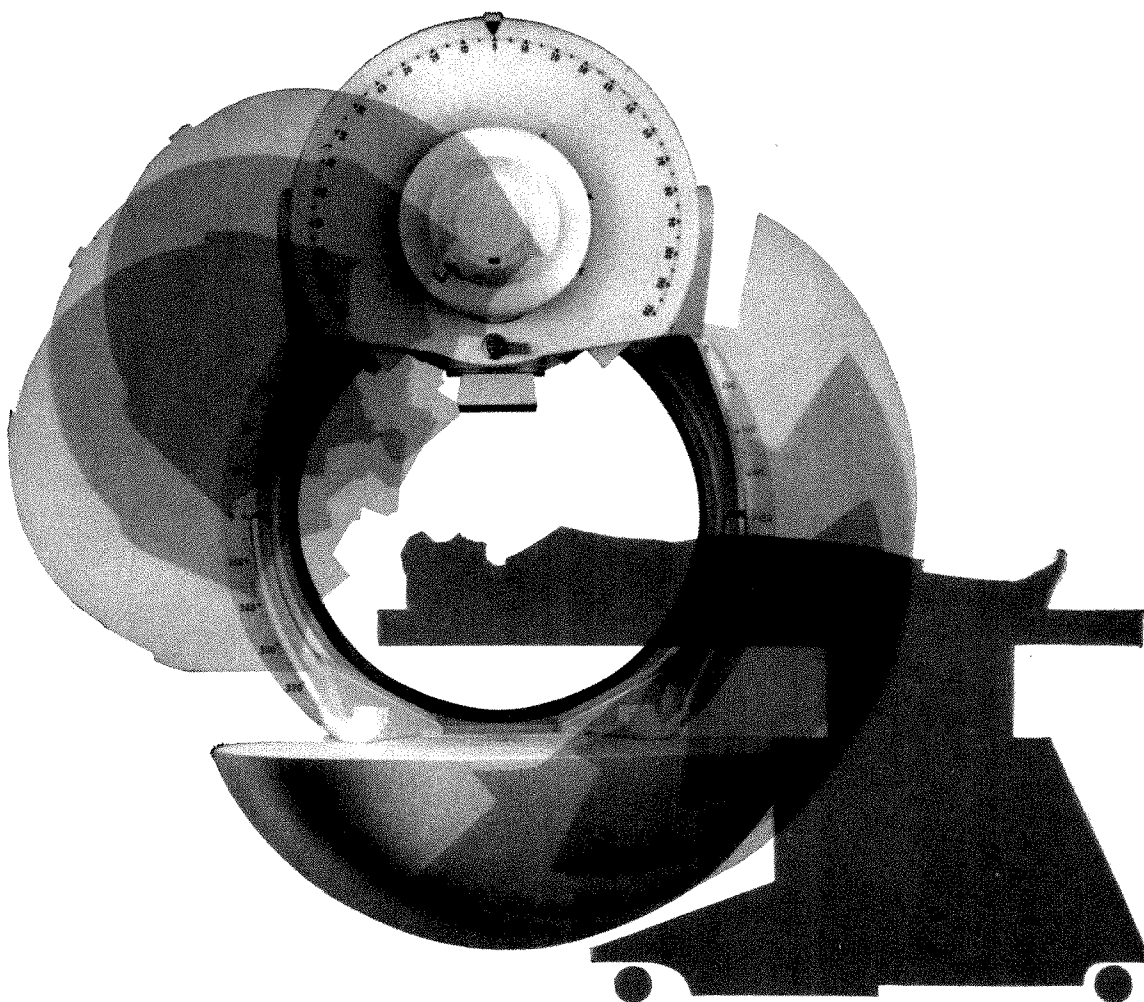
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No. 2

THE AZYGOS VEIN ARCH AND ITS VALVULAR APPARATUS* ANGIOGRAPHIC OBSERVATIONS

By GIULIO TORI, M.D., and G. F. GARUSI, M.D.
BOLOGNA, ITALY

SINCE Busi⁶ and other workers^{27,43} first recorded the roentgenologic morphology of the azygos vein as seen on posteroanterior roentgenograms of the chest, the literature on the roentgen aspects of the vessel in both normal and pathologic conditions has been considerably enriched.

The characteristic "pumpkin seed" image lying in the low paratracheal region near the right bronchus and equal in density to the aorta corresponds, according to the great majority of authors, to the frontal view of the azygos vein arch. Even in normal individuals the image shows variable morphology and dimensions; this may depend, on the one hand, on the various conditions of projection of the vessel and, on the other, on the degree of opacification by the injected medium. Thus, when the patient shifts from a standing to a prone position, the caliber of the vessel increases; this also happens in deep breathing, while the caliber is considerably reduced during the Valsalva maneuver.

In pathologic conditions the azygos vein is considerably enlarged, as, for instance, in

cardiac diseases and extracardiac morbid processes which obstruct the drainage of the superior vena cava into the right heart (Meldolesi²³ and Grilli¹⁷).

Fleischner and Udis¹⁵ emphasize that the increase in size of the azygos vein appears most often in cardiac failure, but they also have observed volumetric increases in the vessel in cases of exudative and constrictive pericarditis. Furthermore, they state that enlargement of the azygos vein almost always appears in tricuspid insufficiency. As pointed out by all the aforementioned authors, the degree of enlargement of the azygos vein may serve as a useful indicator of the functional integrity or of the impaired performance of the right heart.

The most frequent extracardiac lesions which may cause increase in the caliber of the azygos vein are mediastinal tumors or calcifications compressing and occluding the superior vena cava. The dilatation, in this case, is the result of the fact that the azygos system connects the two venous systems of the superior and inferior vena cava. If the occlusion in the superior vena

* From The Radiological Institute of Bologna University.

cava is above the insertion of the azygos vein, the venous blood from the head and trunk reaches the right atrium not only through the abdominal veins and the superficial veins of the thorax, but also through the intercostal veins, thus bringing about dilatation of the azygos vein. When, however, the occlusion of the superior vena cava occurs below the insertion of the azygos vein, the blood from the head and trunk reaches the right atrium by reverse flow through the azygos and lumbar veins and then through the inferior vena cava.

Dilatation of the azygos vein may also take place in cases of absence or hypoplasia of the inferior vena cava, as described by Downing,¹¹ or in patients with occlusion of the inferior vena cava, as reported by Stauffer and colleagues.³⁵ Sometimes the increase in size assumes the aspect of a true aneurysm, as in the case described by Schmidt,³² where the dilatation was such as to simulate a mediastinal tumor. Observations of a similar nature have been described by other authors (Sayer *et al.*,³¹ Leigh *et al.*,¹⁹ and Shuford and Weens³⁴).

In both normal and pathologic conditions the study of the arch of the azygos vein may be carried out in more detail by laminagraphy. Gemignani¹⁶ and Mainoldi,²² who have studied the vein laminagraphically, especially in normal subjects, affirm that the vessel is visible only in those cases where it is surrounded by an aerated parenchyma. In cases of more or less extensive atelectasis, fibrous and infiltrating parahilar processes of vast extent, and serious thickening of the mediastinal pleura, the vessel cannot be seen.

Motta²⁴ calls attention to other particulars which concern the movement and displacement of the vessel in pathologic conditions. In cases of infiltrating or cavitary parenchymal lesions of the right upper lobe, the arch of the azygos vein is considerably displaced laterally with respect to the tracheobronchial angle, which is its normal seat. A certain degree of upward displacement may also be noted—very slight in some cases while in others amount-

ing to as much as 3-4 cm. Conversely, in case of pneumothorax, the arch of the azygos vein may appear to be medially displaced towards the mediastinum.

To summarize, plain roentgenography and laminagraphy can visualize the arch of the azygos vein in the vast majority of cases, whether normal or pathologic. The roentgen findings obtainable by these studies still leave open to discussion the interpretation of the morphologic aspects and the evaluation of the variations which are met with in certain normal conditions and in pathologic processes.

THE PRESENT STUDY

During angiocardigraphic investigations (standard angiocardigraphy and perosseous azygography) we have collected some observations which we believe are of sufficient interest to merit presentation and which also give a clearer understanding of the above-mentioned problems.

Our observations refer chiefly to the morphology of the terminal portion of the azygos vein, commonly known as the arch of the azygos vein, and to its valvular system seen mostly during angiocardigraphic examinations carried out on subjects afflicted, for the most part, with cardiac or mediastinum-pulmonary diseases. Further information has been collected through perosseous azygography (the direct introduction of a radiopaque medium into the marrow of a rib—generally the posterior segment of the seventh-tenth right or left rib—by means of a sternal puncture needle percutaneously inserted into the rib).

These observations are the result of a study of approximately 150 angiocardio-grams and 100 azygograms.

THE ARCH OF THE AZYGOS VEIN

The arch of the azygos vein begins at the level of the fourth to sixth vertebra, bending forward and describing a downward concave arch which can be of varying degree. We have observed: (1) hooklike arch; (2) small radius arch; and (3) large radius arch. Of these three types, the most frequent

seem to be the last two (Fig. 1, *A* and *B*). Numerous transitional forms, however, exist. More or less pronounced kyphosis of the spine does, of course, influence the de-

gree of curvature, as does the anteroposterior diameter of the thorax and the position and orientation of the heart. In a certain number of cases the terminal por-

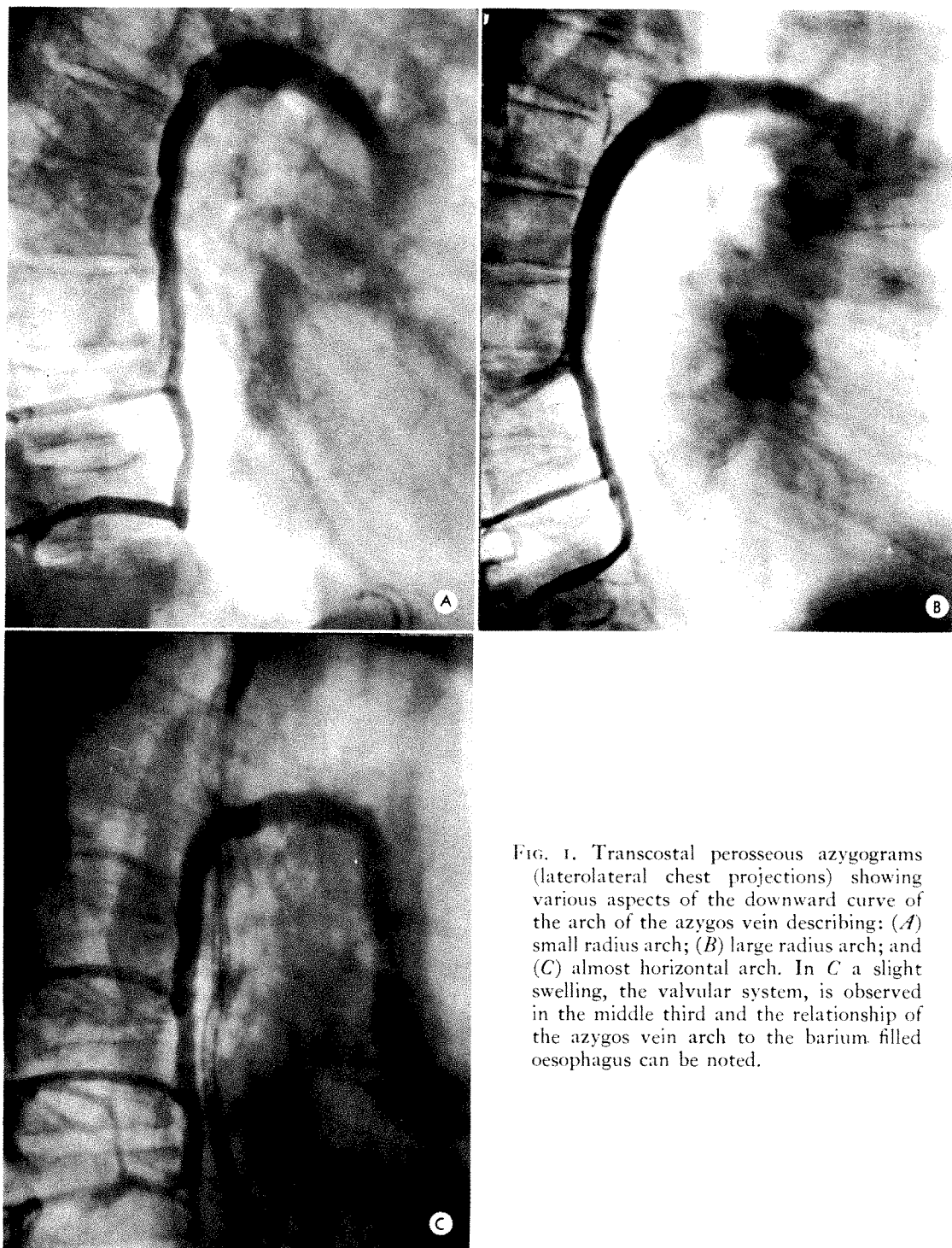


FIG. 1. Transcostal perosseous azygograms (laterolateral chest projections) showing various aspects of the downward curve of the arch of the azygos vein describing: (*A*) small radius arch; (*B*) large radius arch; and (*C*) almost horizontal arch. In *C* a slight swelling, the valvular system, is observed in the middle third and the relationship of the azygos vein arch to the barium filled oesophagus can be noted.

tion of the azygos vein has no downward concave curvature, but an almost horizontal course (Fig. 1C).

The downward concave course of the arch in a sagittal direction is easily seen on the laterolateral chest roentgenogram. In order to obtain a more exact idea of the morphology and course of the vessel, these findings, however, must be considered along with those observed on the anteroposterior roentgenograms. By so doing, we noted that, in the majority of cases, the course of the arch also shows a medially concave curve; *i.e.*, as demonstrated by the brilliant anatomic research of Andreassi² (Fig. 2), the arch first passes laterally from its point of origin and then, having traversed the

right main bronchus, it proceeds medially downward (Fig. 3A). This projects on the anteroposterior roentgenogram—due to the superimposed shadow of part of the azygos vein in its medial curve and the adjacent anterior segment which bends from the outside towards the inside and downwards—as an oval-shaped image, with the longer axis lying in a vertical or oblique direction (Fig. 3B). Less frequently, when the arch is almost horizontal and does not describe a true medially concave curve, in the frontal view the vessel appears round in shape and is usually situated considerably to one side of the spinal column (Fig. 3, C and D). In such cases, the azygos vein arch actually follows a rather long, clearly lateral course initially and then, continuing on an entirely sagittal plane, it empties into the superior vena cava.

The caliber of the arch, of course, increases, though slightly, from the point where the vessel leaves the anterior edge of the dorsal spine until it empties into the superior vena cava. In some cases, however, true increase is not evident, and the terminal portion of the azygos vein may show an almost uniform caliber. The valvular system, due to its relative continence, causes a variation in caliber as evidenced by the fact that the postvalvular part, that is, the segment between the valves and the insertion in the superior vena cava, shows an appreciably greater caliber than the posterior part.

INSERTION OF THE AZYGOS VEIN

The azygos vein drains into the upper third of the superior vena cava, usually 2–3 cm. from the vessel origin as a result of junction of the two innominate veins; an insertion at a higher level is rare. It is generally found at a lower level than both the peak and the posterior point of origin of the arch. Less frequently the insertion is found at the same level or slightly above the posterior point of origin.

The azygos vein almost always opens into the posterior wall of the superior vena cava (Fig. 4A); rarely does it open into its

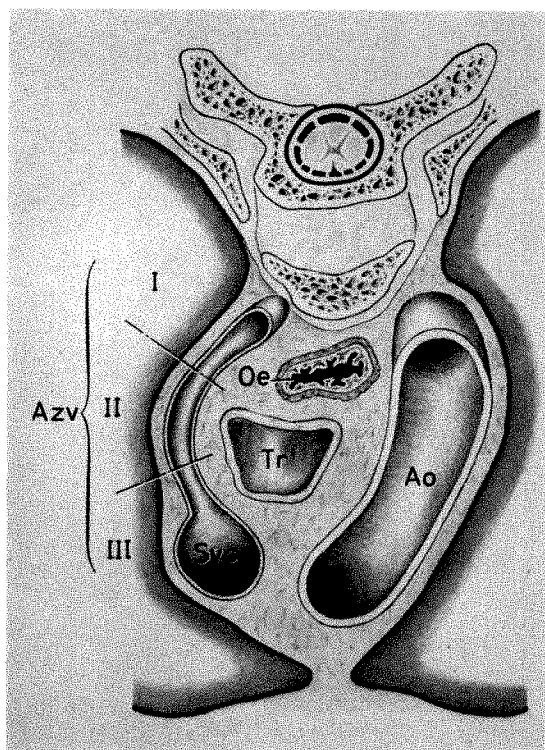


FIG. 2. Drawing (modified from Andreassi²) of a transverse section of thorax at the level of the fourth dorsal vertebra illustrates how the arch describes a medially concave curve, first passing laterally from the point of origin (I, posterior segment), then in a forward direction (II, intermediate segment), and, finally, turning inward and downward (III, terminal segment). (Ao, aorta; Azv, azygos vein; Oe, oesophagus; Svc, superior vena cava; Tr, trachea.)

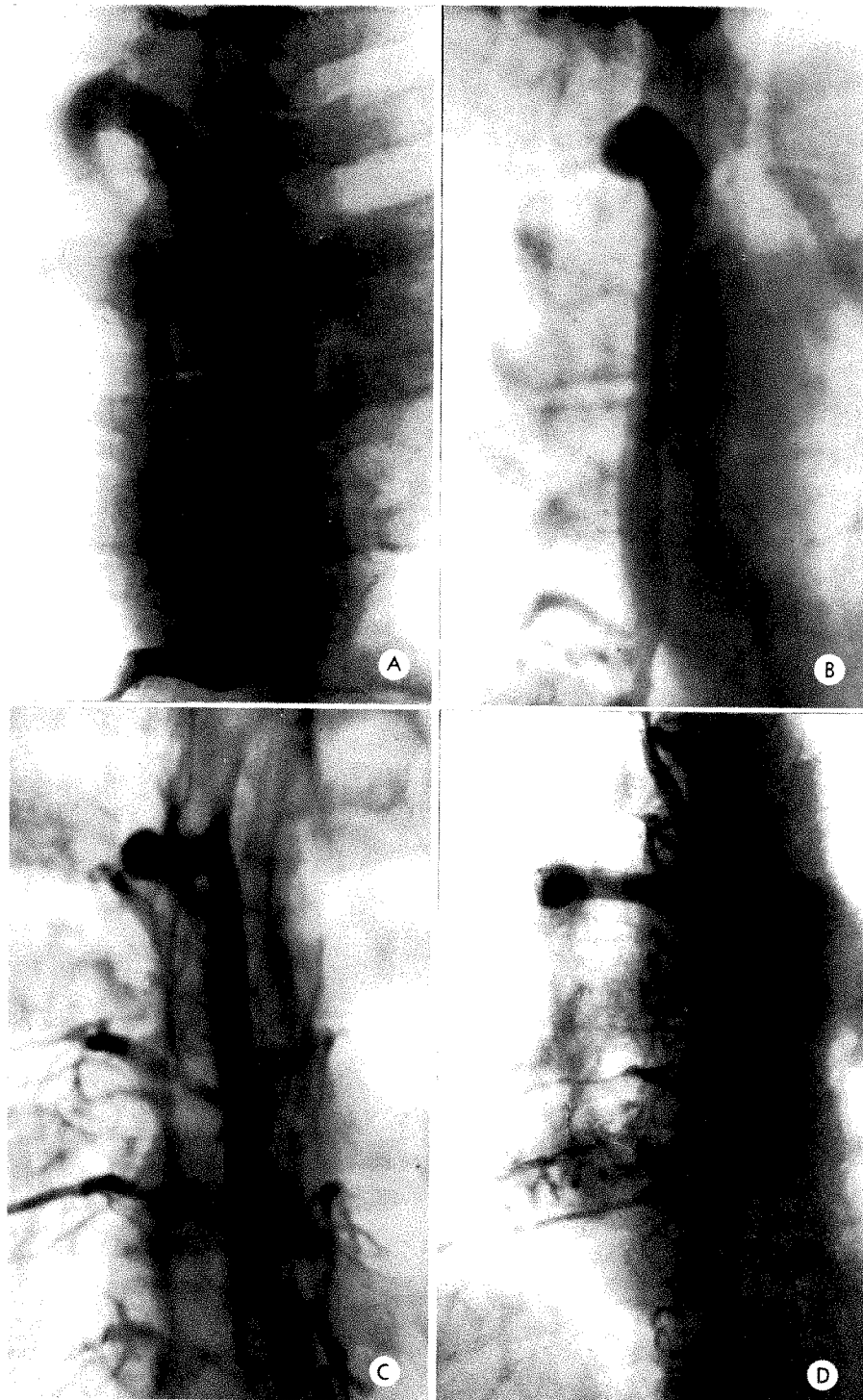


FIG. 3. Posteroanterior transcostal perosseous azygograms. (A) The azygos vein arch describes two curves, one with downward concavity and the other with medial concavity. (B) In the frontal view the arch casts an oval shadow with the longer axis lying obliquely. (C and D) Two cases in which the azygos vein arch first passes outward, then forward horizontally without a true medial concave curve; it assumes a rounded shape in the frontal view.

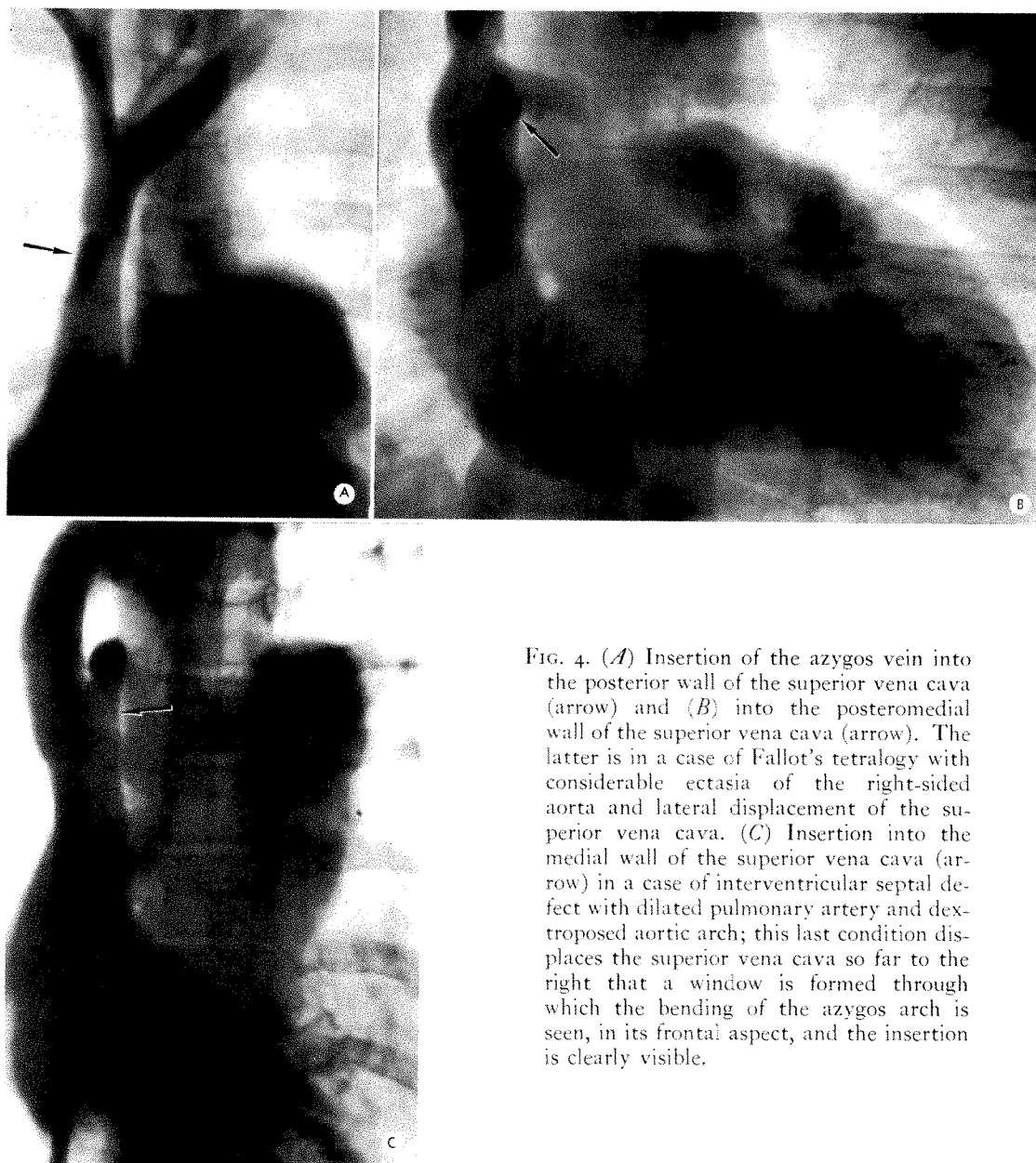


FIG. 4. (*A*) Insertion of the azygos vein into the posterior wall of the superior vena cava (arrow) and (*B*) into the posteromedial wall of the superior vena cava (arrow). The latter is in a case of Fallot's tetralogy with considerable ectasia of the right-sided aorta and lateral displacement of the superior vena cava. (*C*) Insertion into the medial wall of the superior vena cava (arrow) in a case of interventricular septal defect with dilated pulmonary artery and dextroposed aortic arch; this last condition displaces the superior vena cava so far to the right that a window is formed through which the bending of the azygos arch is seen, in its frontal aspect, and the insertion is clearly visible.

medial wall. This latter occurrence can only be demonstrated when the superior vena cava is almost completely rotated and displaced outwards by the aorta, dextroposed, as in congenital heart defects, or when there is a considerable degree of ectasia (Fig. 4, *B* and *C*). In these instances, the medial insertion is more apparent than real, being the result of a change of position of the superior vena cava. We have ob-

served 1 such case. The patient had a rotation defect of the cardiac cavities and an ascending aorta displaced to the left; the very large azygos vein emptied posterolaterally into the superior vena cava.

VALVES OF THE ARCH OF THE AZYGOS VEIN

These are generally two in number and are situated halfway along the arch at the

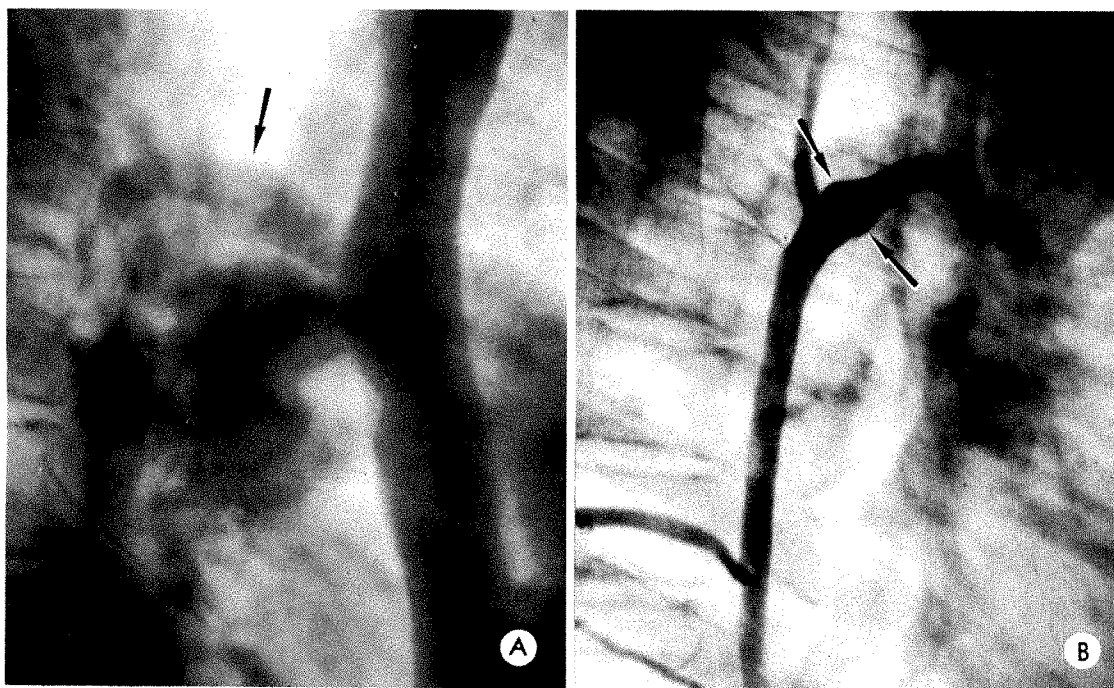


FIG. 5. Valves of the arch of the azygos vein. (*A*) Opacification of the arch by reflux during angiocardiology in the laterolateral projection. The valves (arrow), in the middle third of the arch, are visible due to the accumulation of opacified blood in the pockets posterior to the valves. (*B*) The valves (arrows), in the posterior third of the arch, are visualized during perosseous azygography.

point where it crosses the right main bronchus, or in the posterior third of the arch (Fig. 5, *A* and *B*). (We have never observed the valvular system in the anterior third of the arch.) In the laterolateral projection the vessel shows a considerable swelling at this point, caused by the accumulation of radiopaque blood in the pockets posterior to the valves. These findings confirm the anatomic data provided by Poirier and Charpy,²⁹ as well as by Sylwanowicz.³⁸

In the anteroposterior projection the valves cast a characteristic roentgen shadow. As they are situated in the intermediate segment of the azygos arch, they assume what we have called a "coffee bean" appearance (Fig. 6, *A* and *B*) in which the two halves of the shadow, not really oval but almost round, correspond to the two pockets filled with contrast medium, while the central dividing line corresponds to the slit between the two valvular edges. These latter may be of equal or unequal size; their

orientation, and also the slit between them, is variable, so that they may appear in a vertical, oblique or almost transverse position.

The valves, when the superior vena cava is well opacified, are visualized within the shadow of the latter; however, they may also protrude eccentrically when the intermediate segment of the arch is at some distance from the insertion of the azygos vein into the superior vena cava.

Another very rare image observed in the anteroposterior projection, which we have called "snake mouth" appearance, occurs when the valves, instead of being visualized in the frontal aspect, are viewed almost lengthwise at a considerable angle (Fig. 6C). This is seen when the valves, instead of being located in the intermediate segment which has a relatively sagittal course, are located in the posterior segment which has a mediolateral course.

In almost all cases observed by us the valves were double (Fig. 6, *A* and *B*);

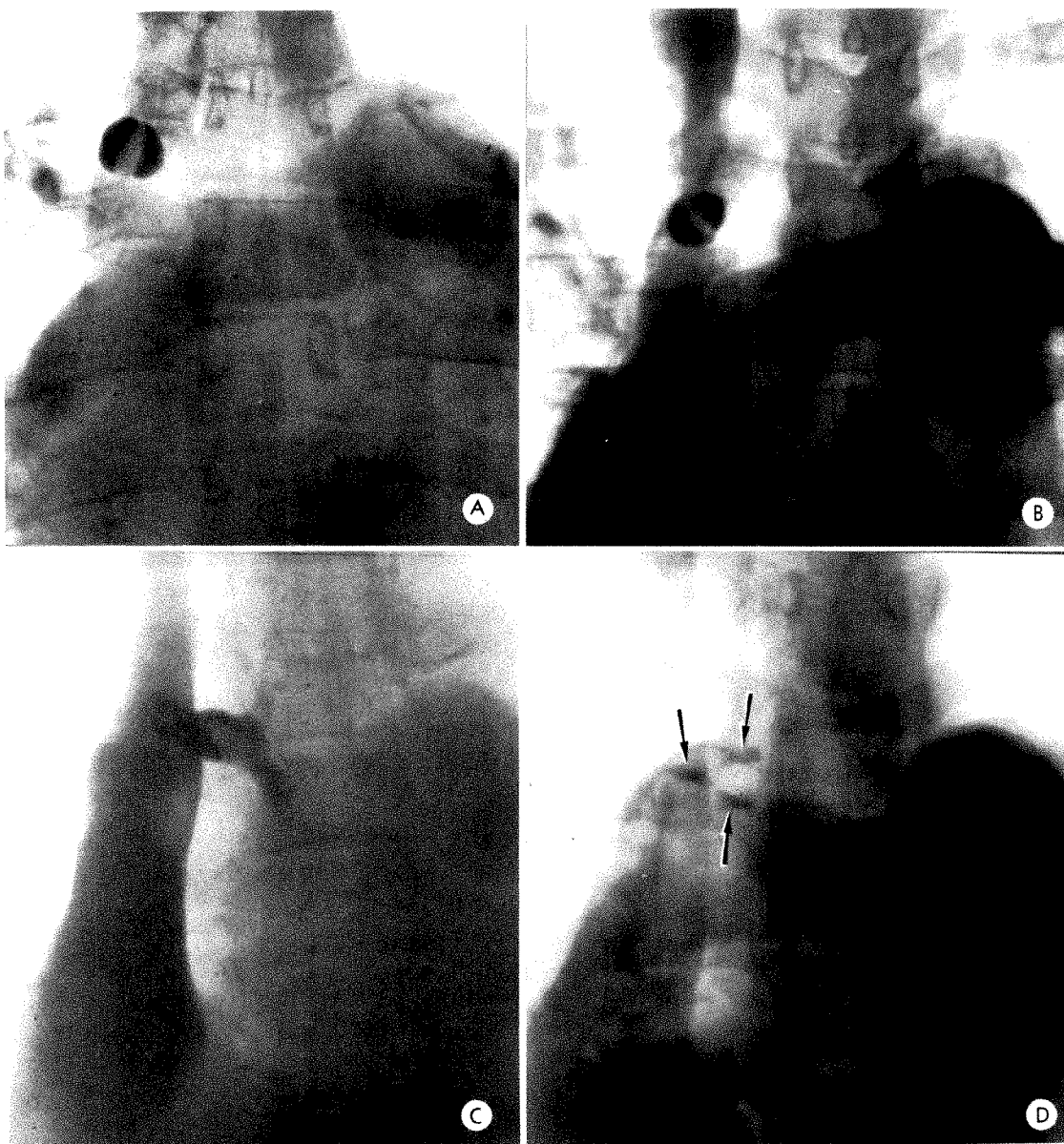


FIG. 6. The valves of the azygos vein arch are visualized in anteroposterior projection of the thorax by reflux during angiocardigraphy. (*A* and *B*) The "coffee bean" appearance: the valve borders, equal in size, may have (*A*) an almost vertical or (*B*) a transverse position. (In both of these examples the valvular system is seen within the shadow of the opacified superior vena cava.) (*C*) The "snake mouth" appearance of the valves in an aged patient with a right paracardiac tumor pressing on the sinus of the venae cavae and the right atrium. Partial incontinence of the valvular system can be noted. (*D*) Azygos valves with three borders (arrows).

triple valves were rarely seen (Fig. 6*D*). The marked agreement with the findings of Sylwanowicz³⁸ on cadavers must here be noted, since he found double valves in the majority of the 44 subjects he studied; triple and single valves were less frequent.

In our observations of reflux into the azygos vein arch during angiocardigraphy; we found cases where the valves were not evident, possibly due to their rudimentary structure.

These observations refuted the theory of

Poirier and Charpy,²⁹ and upheld that of Sylwanowicz³⁸ concerning the continence of the valvular system of the azygos vein arch. This function may be evaluated on the basis of reflux of the blood containing the contrast medium. We have noted cases in which the reflux passed the valvular system opacifying the posterior segment of the arch, and others in which the valves seemed to close. In other words, it would be more correct to speak of a relative patency of the valves of the azygos vein arch. The best visualization of the valves was obtained in cases of stenosis-insufficiency type lesions of the tricuspid valve. In such cases the "coffee bean" shadow remained visible as long as ten to fifteen seconds after the azygos vein arch itself became empty of blood containing opaque material. However, we were unable to visualize the valvular system in mitral disease and in cardiac failure. This would suggest then, that roentgen visualization of the valvular system of the arch of the azygos vein may constitute an indication of right endoatrial stasis caused by impeded emptying through the tricuspid valve rather than by cardiac failure.

POSITIVE AND NEGATIVE IMAGES OF THE AZYGOS VEIN IN ANTERO- POSTERIOR PROJECTION

The positive image in the frontal view corresponds to the arch of the azygos vein, when it is filled with contrast medium. In most cases the shadow has an oval shape with the longer axis vertical or oblique. This, the most frequent aspect, is the result of a frontal image of the intermediate segment of the arch combined with the shadow of the anterior segment (Fig. 3*B*; and 4*A*). When the arch has a predominantly horizontal course, without presenting a true medial concavity, the positive image is rounded in shape (Fig. 3, *C* and *D*).

The negative image appears during angiocardigraphy carried out intravenously according to the standard procedure; presumably it is due to penetration into the superior vena cava of a flow of blood from

the azygos vein which does not contain contrast medium. Such a finding, which according to some authors^{4,8} is fairly frequent, is indicative of the true position of the mouth the azygos vein in the superior vena cava.

We have seen a remarkable number of such negative images. The morphologic basis and the dimensions of these so-called negative images are variable. Thus, while in some congenital or acquired cardiac defects the shadow appeared relatively small and round (Fig. 7, *A* and *B*), in another case of rotation of the cardiac cavities the mouth was considerably dilated (Fig. 7*C*); in yet another (tricuspid stenosis-insufficiency with considerable dilatation of the superior vena cava) the mouth was oval-shaped with the longer diameter lying obliquely, and within the shadow was seen another smaller, rounded image, perhaps the frontal view of the arch.

The observation of negative images of the mouth combined with reflux visualization of the arch is very rare (Fig. 8*A*). An explanation of the mechanism for this phenomenon seems to be offered by observations in other cases where, both in the laterolateral and the anteroposterior projections, the contrast medium was seen to spread out along the vessel wall, while the central part of the lumen showed no opacification (Fig. 8, *B* and *C*). The course of events might, therefore, be as follows: after a first reflux of opaque blood from the superior vena cava into the azygos vein, a central flow of blood in the vessel, without contrast medium, makes the central zone of the azygos vein appear lighter.

SUMMARY

1. Our angiographic observations of the arch of the azygos vein and its valvular system may be considered from two viewpoints: (a) as a corroboration of the findings on the arch of the azygos vein at post-mortem examination; and (b) as the basis for a more detailed interpretation of the roentgen findings of the azygos vein detect-

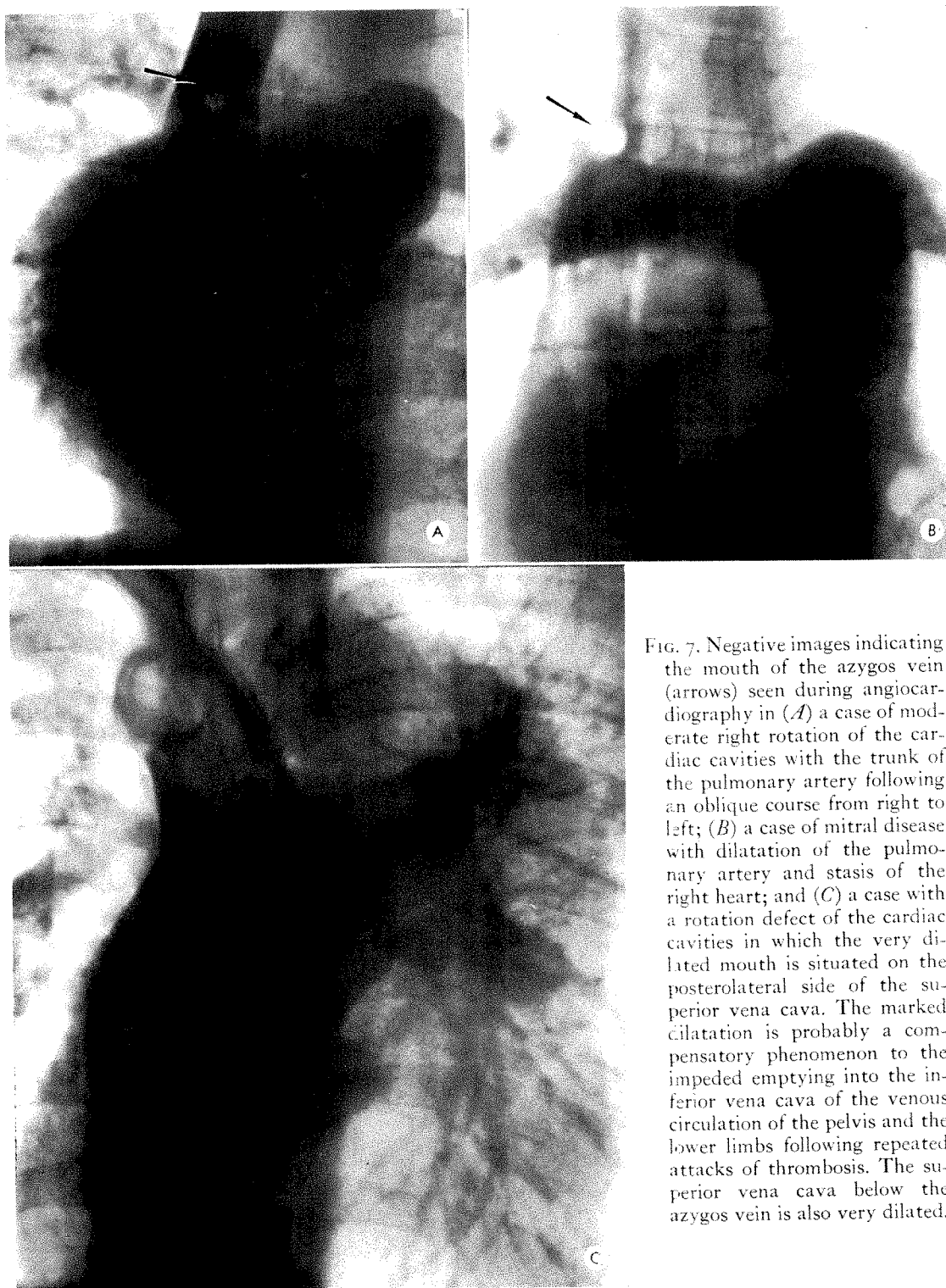


FIG. 7. Negative images indicating the mouth of the azygos vein (arrows) seen during angiocardiology in (A) a case of moderate right rotation of the cardiac cavities with the trunk of the pulmonary artery following an oblique course from right to left; (B) a case of mitral disease with dilatation of the pulmonary artery and stasis of the right heart; and (C) a case with a rotation defect of the cardiac cavities in which the very dilated mouth is situated on the posterolateral side of the superior vena cava. The marked dilatation is probably a compensatory phenomenon to the impeded emptying into the inferior vena cava of the venous circulation of the pelvis and the lower limbs following repeated attacks of thrombosis. The superior vena cava below the azygos vein is also very dilated.



FIG. 8. (A) Negative image of the mouth of the azygos vein (left arrow) clearly seen during reflux of the contrast medium into the arch and the valvular system (right arrow). (B) "Rail" appearance of the azygos arch (arrows) seen in the laterolateral projection. (It is suggested that this effect is produced by dilution of the contrast material with nonopacified blood flowing in the center of the vessel and the residue of the contrast medium spreading along the walls.) (C) The "rail" appearance seen in the anteroposterior projection. The mouth of the azygos vein (arrow) resembles a ring.

able on conventional roentgenologic examinations of the thorax.

2. In most cases the arch of the azygos vein shows a downward concave curvature as well as a medial concavity. In the anteroposterior projection of the chest, due to superimposition of shadows, an oval-shaped image with a longer vertical or oblique axis is seen. Less frequently, when the azygos arch runs horizontally without medial curvature, the image assumes a rounded appearance.

3. The insertion of the azygos vein is found on the posterior wall of the superior vena cava at a level usually lower than the point of posterior origin of the arch itself. Insertion on the medial side of the superior vena cava is rare and is found only when the vena cava itself is displaced outward due to pathologic causes.

4. The valvular system of the azygos vein is found about halfway along the arch or in the posterior third; the valves usually are double and, in the frontal view (anteroposterior projection), they show a characteristic "coffee bean" appearance. The

valve edges may be assumed to be relatively continent.

5. The *positive image* of the arch of the azygos vein in the anteroposterior projection frequently has an oval or, more rarely, a rounded shape.

6. There are however, also, *negative images*, presumably due to flow of blood not containing contrast medium from the azygos vein into the injected superior vena cava. Images of this kind may vary both in underlying morphology and in dimension; they seem to correspond exactly to the mouth of the azygos vein in the superior vena cava.

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DILATATION OF THE HEMIAZYGOS VEINS IN SUPERIOR VENA CAVAL OCCLUSION SIMULATING MEDIASTINAL TUMOR*

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IN 1938, soon after the Robb-Steinberg method of angiocardiology had been described, there appeared a report of the case of a young woman with a markedly dilated hemiazygos vein and stenosis of the superior vena cava. A lung abscess had developed in this patient following Hodgkin's disease which had been treated with radiation therapy.^{21,22,26} Largely dilated hemiazygos veins had also been demonstrated in 1954 in a patient with superior vena caval occlusion due to fibrous mediastinitis who had been treated by the insertion of a homograft bypass.¹² Subsequently, 2 more patients with left mediastinal masses due to venous collaterals because of superior vena caval occlusions were encountered. Indeed, in the first case herein reported, that of an asymptomatic thirty-five year old man, the characteristic appearance of the shadow in the left mediastinum suggested the diagnosis of dilated hemiazygos veins and superior vena caval occlusion; venous pressure and angiocardigraphic studies confirmed it. Barrett² deserves credit for first describing a large series of cases with hemiazygos venous engorgement which simulated mediastinal tumors when the vena cava became occluded owing to idiopathic mediastinal fibrosis.

The purpose of this report is to emphasize that left mediastinal widening may be caused by dilatation of the hemiazygos venous system because of long standing vena caval occlusion and to point out that the diagnosis of this condition can readily be confirmed by venous pressure and angiographic studies.

REPORT OF CASES

CASE 1. *Dilated hemiazygos system in an asymptomatic man with superior vena caval occlusion of unknown etiology.* A thirty-five year old warehouse man (N.Y.H. No. 797068), referred by Dr. Peter Dineen, was admitted on June 3, 1958, with a chief complaint of an ulcer of the left leg of two months' duration. Four years prior to admission to another hospital, he had had subtotal thyroidectomy for suspected toxic goiter, and histologic study of the excised specimen had revealed a toxic adenoma. Anterior chest wall varicosities had been noted on physical examination, but no collateral veins or jugular distention had been encountered at the time of thyroidectomy. A roentgenogram of the chest, however, had not been made.

The patient had been well until ten weeks prior to admission to The New York Hospital, when he accidentally scratched the left medial surface of the upper calf with a nail file. A week after this, he noted tenderness, erythema, and purulent drainage at the site of injury. Despite treatment, the lesion enlarged although there were no constitutional symptoms.

On examination, the patient appeared well-developed and well-nourished. An 8 by 5 cm. irregular, ulcerated area with islands of epithelium, a crusted necrotic border, and a base of granular tissue was noted in the left lower calf. Varicose veins of the left leg and dilated veins of the upper abdominal mass were prominent. Culture of the exudate from the leg ulcer grew out *Staphylococcus aureus hemolyticus*. Roentgenograms of the chest revealed a nodular mass in the left mediastinum (Fig. 1, A and B). Distended right jugular and upper thoracic veins were then noted. Angiocardiology on June 10, 1958, demonstrated occlusion of the left innominate vein with tremendous hemiazygos vein dilatations (Fig. 1, C and D).

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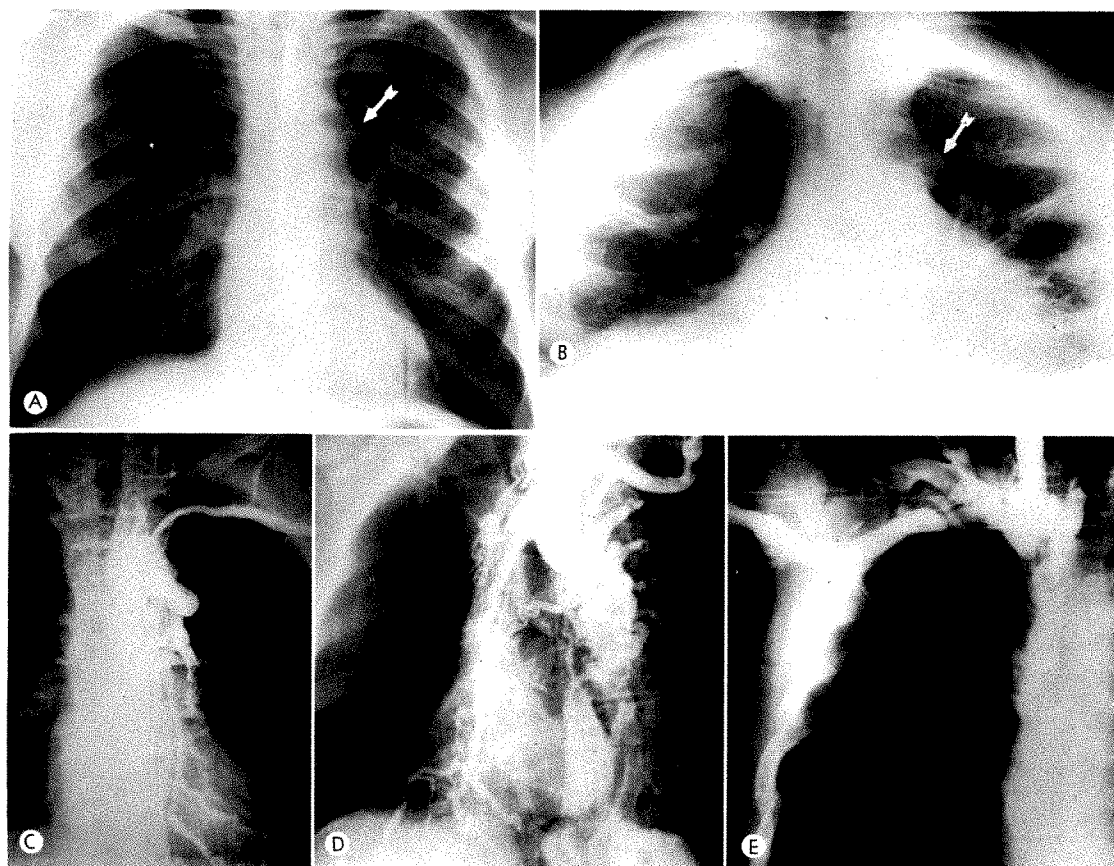


FIG. 1. Case 1. (A) Frontal teleroentgenogram showing widening of the right superior mediastinum with a small left mediastinal mass (arrow). (B) Lordotic frontal roentgenogram more clearly reveals the left mediastinal shadow (arrow). (C) Frontal angiogram (left arm injection) demonstrates that the dilated tortuous hemiazygos venous channels are responsible for the left mediastinal mass. (D) Left anterior oblique roentgenogram showing the tremendously dilated hemiazygos system finding its way to the inferior vena cava. (E) Frontal angiogram (right arm injection) showing the superior vena caval occlusion and that the widened right mediastinal shadow is due to the dilated right innominate vein.

Venous pressure studies on June 14, 1958, yielded these results: the right arm, 390 mm. H₂O; left arm, 370 mm. H₂O. After hepatic pressure these rose to 560 mm. H₂O. After bed rest, the greater saphenous vein was ligated, the veins of the left leg were stripped, and the edges of the ulcer were excised. Skin grafts were placed over the ulcer four days later. On June 14, angiocardigraphy via injection into the right arm demonstrated superior vena caval occlusion (Fig. 1E). He was discharged on July 2, 1958, but returned in September and November of 1959 because of recurrence of the left leg ulcer, which was again treated with skin grafting. The patient did not return for follow-up studies.

CASE II. Hugely dilated hemiazygos veins due to vena caval thrombosis of undetermined etiology. A thirty year old Negro nurse (N.Y.H. No. 590528) was admitted on March 14, 1959, complaining of headaches, cough, and pain in the right arm. Two years prior to admission (October, 1957) while living in Bermuda, the patient had had a streptococcal sore throat and had been treated with multiple antibiotic drugs. She had developed periaural and periorbital edema, oliguria, and blurred vision, all of which had been attributed to a penicillin reaction. Because of transient albuminuria, nephritis had also been suspected. On a salt free diet and limited fluids and calories, she had lost 40 pounds. However, blood pressure determina-

tions over a five year period had been normal, averaging 120/75 mm. Hg. During an examination in the gynecology service of this hospital on July 15, 1958, one observer had noted that the neck was edematous. However, urinary studies (concentration and dilution tests and blood urea nitrogen) had been normal, and so dilatation and curettage of the uterus for metrorrhagia was performed.

Physical examination on admission to this hospital in March, 1959, revealed puffiness of the face and neck. The lungs were clear and the heart was normal. The blood pressure was 120/80 mm. Hg. Laboratory data were normal except for elevation to 340 mm. H₂O of the venous pressure in both arms. Roentgenography of the chest (Fig. 2, *A* and *B*) disclosed a bulge in the left mediastinum just below the aortic knob. Angiocardiography via the left arm with dilute contrast material, performed on March 26, 1959, revealed superior vena caval occlusion with marked left hemiazygos venous collaterals (Fig. 2, *C*, *D* and *E*). On April 2, 1959, repeat angiocardiographic studies employing dilute contrast material injected via the right arm again showed complete occlusion of the superior vena cava (Fig. 2, *F* and *G*). Following this, anticoagulant therapy was begun and has been maintained. At a recent visit to the clinic (December, 1960), the patient reported that she was able to satisfactorily perform house work and to care for her

daughter, although she still showed venous engorgement of the face, neck, upper extremities, and thorax.

DISCUSSION

Obstruction of the superior vena cava, especially if the collateral circulation is inadequate, produces alarming symptoms. The venous engorgement causes turgor of the face, arms and upper thorax, ruddy cyanosis and distress on lying flat. Cerebral anoxia resulting from stasis of the cerebral circulation brings on headache, dizziness, and syncope. All these signs and symptoms have become known as the superior vena caval syndrome. When fully established, the clinical picture is striking and can often readily be diagnosed by inspection of the face, trunk, and arms. Considerable information regarding the degree of obstruction of the superior vena caval system, whether partial (stenosis) or complete (occlusion) can be secured by measuring the venous pressure of the upper extremities. A very high pressure over 300 mm. H₂O signifies total occlusion, whereas an elevated reading between 200 to 250 mm. H₂O denotes partial obstruction. In the borderline cases, infrared photography of the face, extremities, and trunk may disclose collateral venous

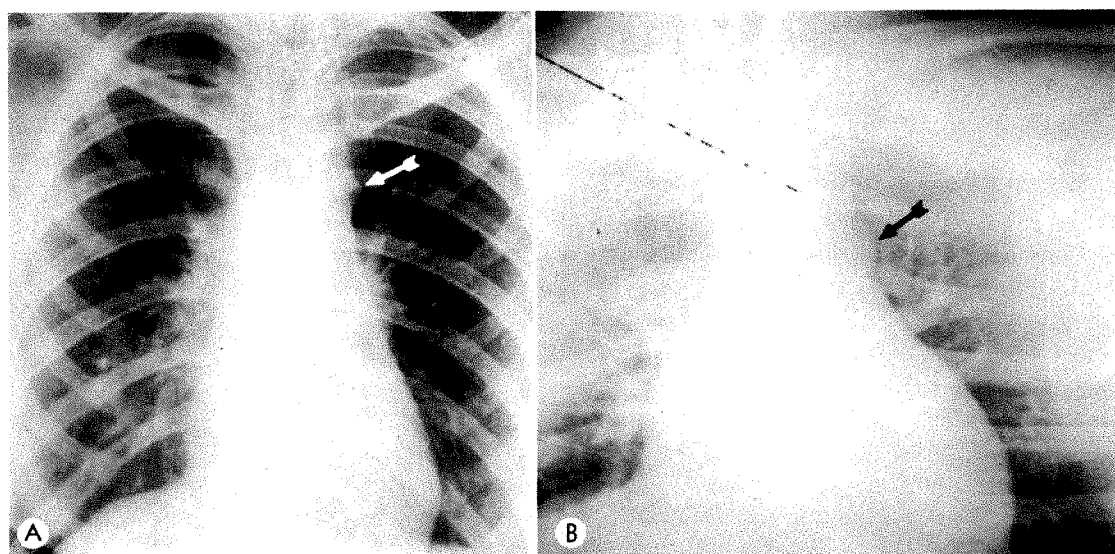


FIG. 2. Case II. (*A*) Frontal teleroentgenogram showing a small left mediastinal mass (arrow). (*B*) Lordotic frontal roentgenogram again showing the mass (arrow).

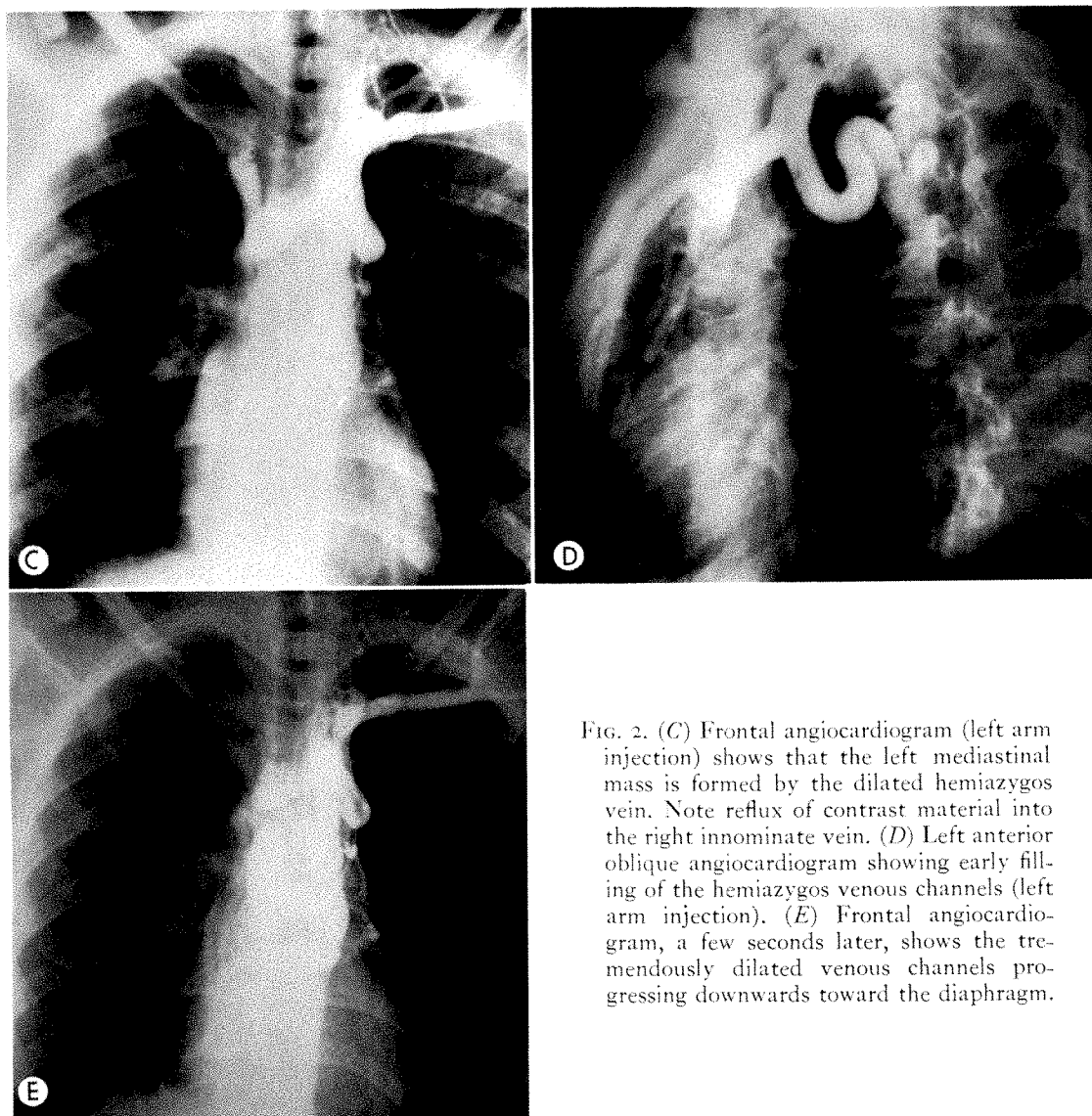


FIG. 2. (C) Frontal angiogram (left arm injection) shows that the left mediastinal mass is formed by the dilated hemiazygos vein. Note reflux of contrast material into the right innominate vein. (D) Left anterior oblique angiogram showing early filling of the hemiazygos venous channels (left arm injection). (E) Frontal angiogram, a few seconds later, shows the tremendously dilated venous channels progressing downwards toward the diaphragm.

channels not readily discernible on inspection (Fig. 3). Visualization of the superior vena caval system by the intravenous injection of contrast material into the arms is the definitive method of showing superior vena caval block, especially of the collateral venous channels.

Intravenous angiocardigraphy by the Robb-Steinberg method, especially when the patient is examined in the erect position, readily shows the venous blood flow into the heart.^{9,21} When bilateral innominate veins are obstructed, especially distal to the superior vena cava, injections into

both arms either simultaneously or else separately in order to localize the sites of stenosis or occlusion are necessary. Since the highly concentrated organic iodides are irritative, angiocardigraphy whenever venous obstruction is suspected should be done with weaker solutions of urokon 30 per cent, rather than with the ordinarily used 70 per cent solution. Also, if the cardiac chambers and the pulmonary arterial and aortic circulations need to be visualized to rule out cardiac and great vessel disease, the medium should be injected via the veins of the leg.

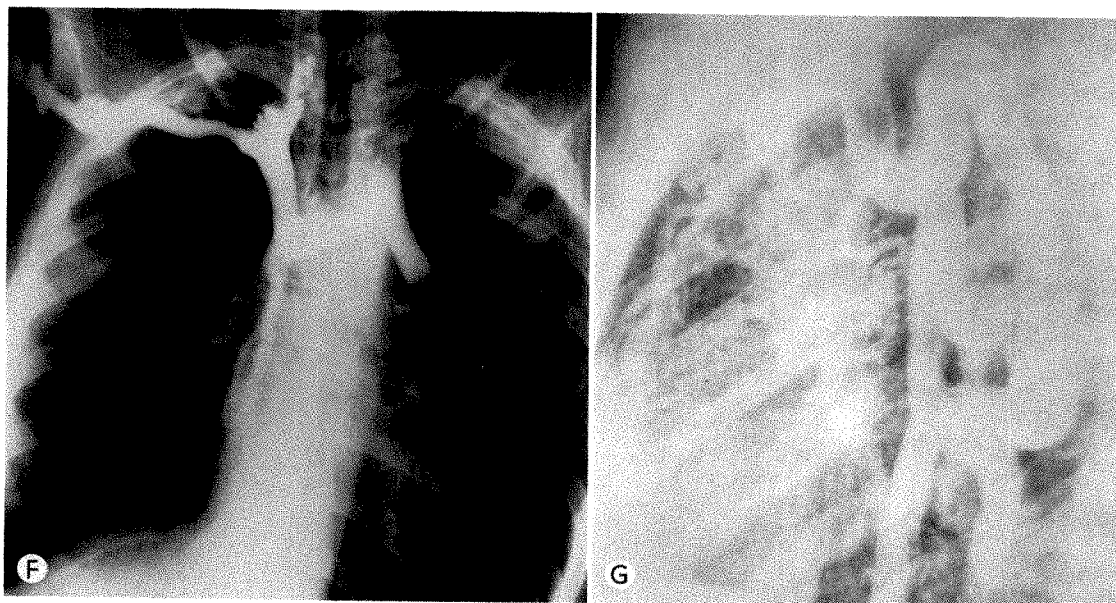


FIG. 2. (F) Frontal angiogram (right arm injection) shows the dilated right innominate vein, superior vena caval occlusion, and passage of the contrast agent into the hemiazygos system. (G) Lateral angiogram (right arm injection) showing the hemiazygos, lower intercostal, and spinal collateral channels plunging towards the inferior vena cava.



FIG. 3. Infrared photograph showing cervical, thoraco-abdominal, and upper arm venous distention due to superior vena caval obstruction (Published by courtesy of Allen E. Weinberg of the Medical Illustrations Laboratory, Veterans Administration Hospital, Coral Gables, Florida.)

Obstruction of the superior vena cava was formerly believed to be rare.^{10,19} Increasing reports of cases describing the syndrome indicate that it is not uncommon.^{4,5,15,16,20} In a series of 55 cases with superior vena caval obstruction reported from The New York Hospital in 1951,²³ 44 patients (80 per cent) had mediastinal neoplasms, 8 had syphilitic aneurysms, and 3 had the syndrome because of thrombosis of the superior vena cava. Ochsner and Dixon,²⁰ in 1936, reviewing 120 cases of superior vena caval obstruction, found 37 per cent due to phlebitis, 29 per cent to external compression (half of these were associated with mediastinal neoplasm), 23 per cent to mediastinitis, and the rest (11 per cent) to unknown causes. Recent experiences at The New York Hospital,^{8,9,27,28,29} elsewhere in The United States,^{4,5,11,24} and in Great Britain³⁰ indicate that carcinoma of the bronchus is the most common cause of superior vena caval obstruction, and is responsible for at least 80 per cent of the cases.

Collateral venous pathways for superior vena caval obstruction have been described by Carlson,⁶ McIntire and Sykes,¹⁹ Klassen

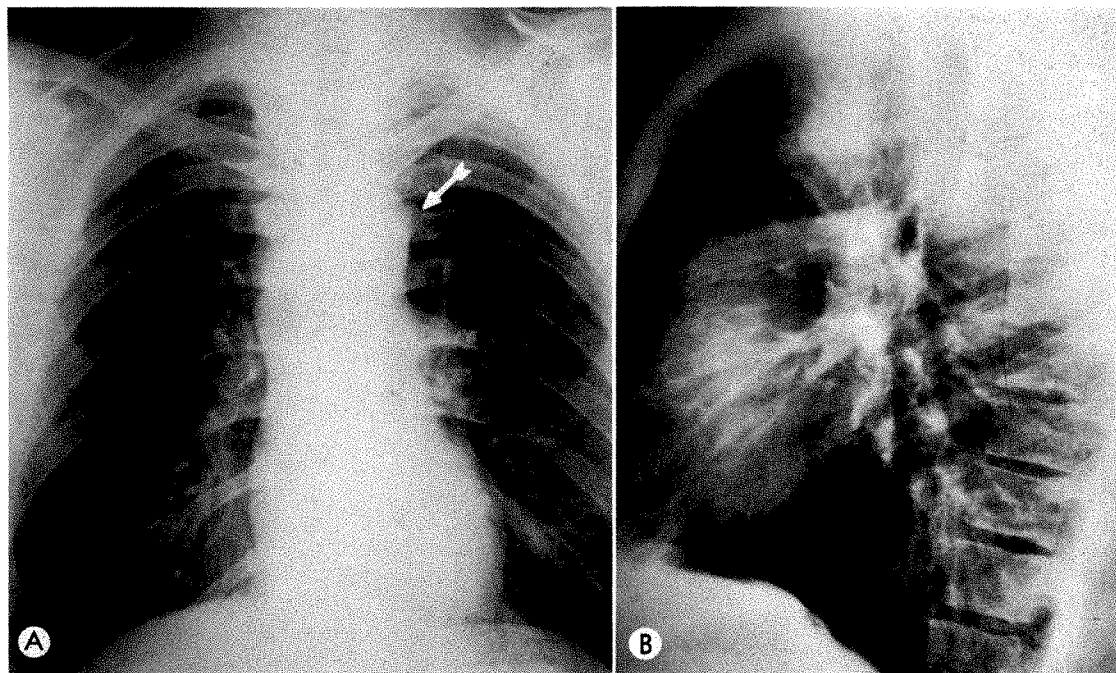


FIG. 4. Complete occlusion of the superior vena cava due to fibrous mediastinitis in a twenty-six year old man. (A) Frontal teleroentgenogram showing widening of the superior mediastinum with a small projection (arrow) from the left mediastinum. (B) Left lateral roentgenogram does not show an obvious mediastinal mass.

et al.,¹⁷ Batson,³ and Abrams.¹ There are 4 routes: (1) the azygos pathway—azygos, hemiazygos, ascending lumbar, and lumbar veins connecting the superior and inferior vena cava; (2) the internal mammary pathway—internal mammary, superior and inferior epigastric, musculophrenic, the intercostal and superficial veins of the thorax, and the iliac vein to the inferior vena cava; (3) the lateral thoracic pathway—lateral thoracic, thoracepigastric, superficial epigastric, superficial circumflex, long saphenous femoral vein, and finally the inferior vena cava; and (4) the vertebrae pathway—innominate, vertebral, intervertebral and vertebral plexus, intercostal, lumbar and sacral veins to the azygos, and internal mammary routes.

Figure 4, A-G demonstrates the value of angiocardiology in the diagnosis and treatment of a patient with superior vena caval occlusion due to fibrous mediastinitis.¹² Preoperatively, the site of vena caval obstruction and the resultant collateral circulation were clearly established (Fig.

4C). Postoperative angiocardiology via simultaneous double injections showed that blood flowed directly from the arm to the right atrium through the patent graft, whereas, on the left side, blood from the left arm still drained into the hemiazygos system and inferior vena cava (Fig. 4, E and F).

The cause of superior vena caval occlusion in the 2 cases herein reported is obscure. In Case 1, the venous collateral circulation of the thorax was well developed and had not produced symptoms. Failure of the left leg ulcer to heal despite vigorous surgical treatment which included ligation and excision of varicose veins and skin grafting suggests that there may exist some underlying disturbance of the venous system producing generalized thrombophlebitis of the mediastinal veins and the lower extremity varicose veins. The second patient (Case II), with superior vena caval occlusion, had thrombophlebitis of the arms. It would appear, therefore, that in both instances the vena caval occlusions

were related to venous thrombosis. The second patient has been receiving anticoagulant therapy.

The patient reported in 1938²⁶ had supe-

rior vena caval stenosis following the development of a lung abscess probably due to Hodgkin's disease which had been treated with roentgen radiation. In another

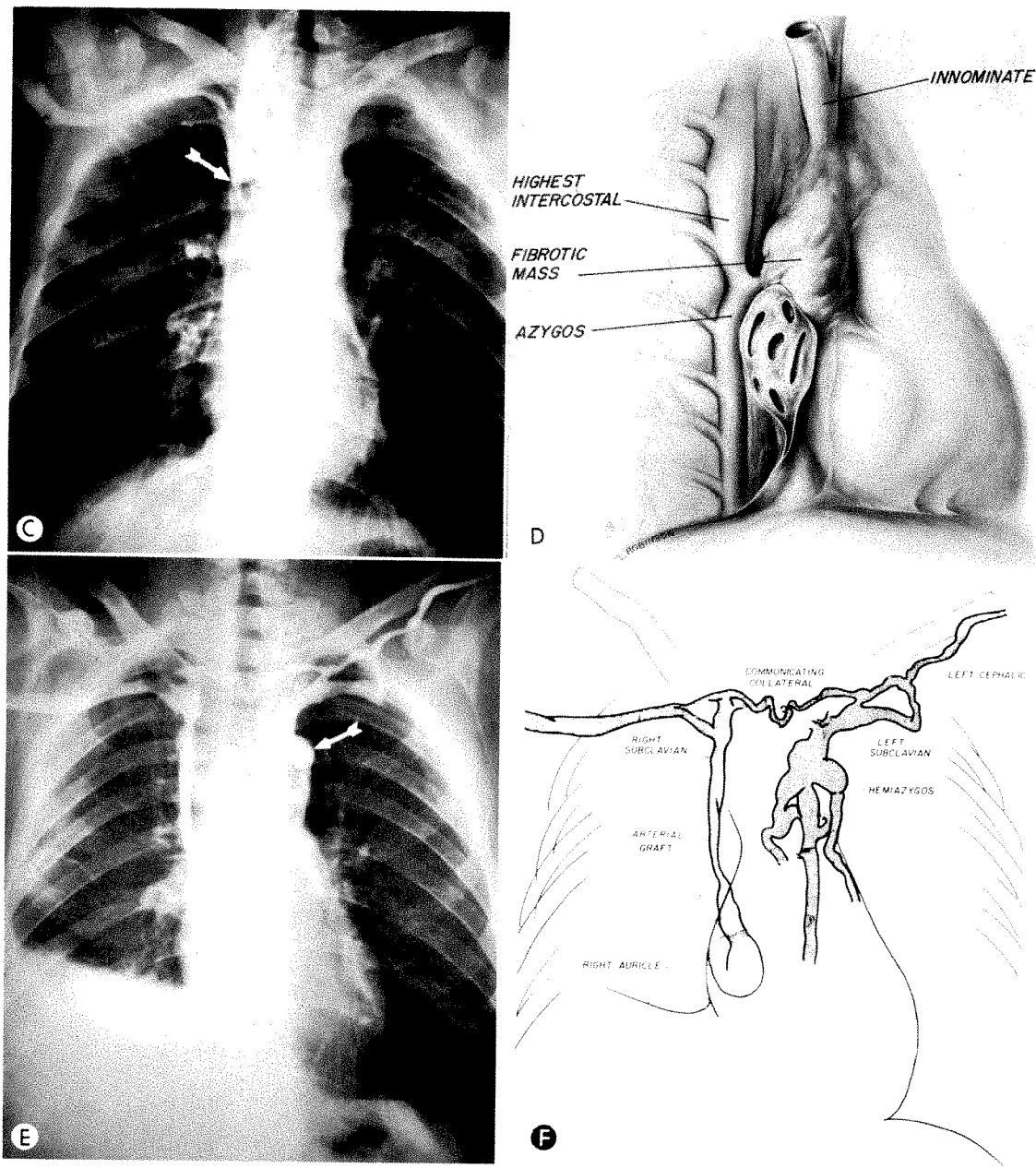


FIG. 4. (C) Frontal angiogram (right arm injection) shows superior vena caval occlusion (arrow). (D) Artist's sketch of operative findings. (E) Postoperative, simultaneous and bilateral angiogram showing the patent arterial graft permitting contrast material to enter the right atrium (unfortunately, this channel subsequently thrombosed). The hemiazygos vein (arrow) is responsible for the left mediastinal mass. (F) Tracing of E. (D and F are republished with permission from *J.A.M.A.*¹²)

patient,¹² the cause of the superior vena caval obstruction was obscure. It was thought to have been secondary to non-specific mediastinitis, probably originating from mediastinal lymphadenitis. Microscopic studies of the mediastinal tissues removed for biopsy had failed to show any evidence of tuberculosis or Boeck's sarcoid (sarcoidosis). The histologic appearance (Fig. 4G) resembled the findings in 3 cases of fibrous mediastinitis reported by Erganian and Wade.¹¹ The homograft installed for bypass of the vena caval occlusion in this case later thrombosed.

The markedly dilated hemiazygos and collateral veins of the 2 newly reported patients (Fig. 1, C,D and E; and 2, C,D,E,F and G) indicate that the superior vena caval occlusions have been long standing. In the superior vena caval obstructions due to carcinoma of the lung, the collateral circulation rarely becomes so plethoric.^{9,27,28,29} This is probably because vena caval occlusion in lung cancer is often a dire and terminal sign; the patient apparently dies before there is time for large collateral channels to develop.

Barrett² proposed that idiopathic mediastinal fibrosis be considered an entity pathologically akin to retroperitoneal fibrosis,⁷ pseudotumor of the orbit, and possibly to Riedel's disease in the thyroid gland. Although chronic fibrous mediastinitis and superior vena caval obstruction have recently been attributed to histoplasmosis,^{18,25} it would seem that in most cases the etiology cannot be determined. Since bypass and replacement grafts have thrombosed and failed to correct vena caval occlusion, surgery has not been effective.² Superior vena caval occlusion due to mediastinal fibrosis is apparently a self-limiting disease, wherein the signs and symptoms of superior vena caval obstruction are mitigated by the development of an adequate collateral circulation.

SUMMARY AND CONCLUSIONS

Dilated, tortuous hemiazygos veins associated with superior vena caval occlusion

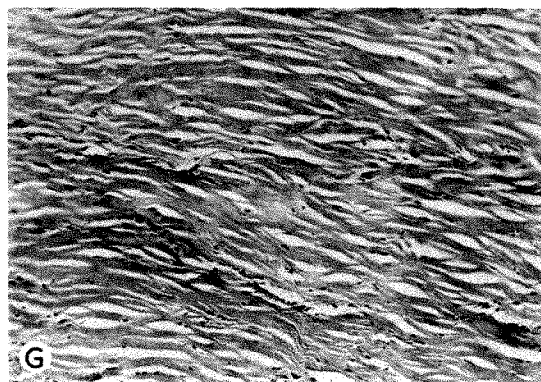


Fig. 4. (G) Histologic section (H. & E. stain $\times 250$) of mediastinal biopsy tissue showing the extensive fibrous reaction.

should be considered in the differential diagnosis of left mediastinal masses. Four patients with vena caval occlusion and dilated hemiazygos veins, 2 previously described and 2 recently observed, showed shadows in the left mediastinum on the conventional roentgenograms. Clinically, all the patients exhibited the signs and symptoms that have become known as the superior vena caval syndrome: swelling of the face, arms and upper thorax, dizziness and headache, and highly elevated venous pressures in both arms. Angiocardiography provided the definitive diagnosis by revealing superior vena caval occlusions and the plethoric and widely dilated hemiazygos system.

Conservative medical treatment with anticoagulant therapy when indicated rather than surgical intervention is recommended for patients with superior vena caval occlusions due to idiopathic mediastinal fibrosis and/or thrombosis. Usually, with passage of time, the development of collateral channels alleviates the symptoms of the vena caval obstruction. Furthermore, homograft and plastic prostheses for bypassing superior vena caval occlusions have proved ineffectual because of the development of thromboses.

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ADDENDUM

Since this paper was submitted for publication, P. F. Partington (Diffuse idiopathic fibrosis, *Am. J. Surg.*, 1961, 101, 239-244) has reported the case of a thirty-nine year old man with mediastinal and retroperitoneal fibrosis who had extensive venous thrombosis and collateral venous circulation. Partington, too, favors the idea that idiopathic fibrosis of the thoracic and abdominal cavities are clinical entities.²

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EXPERIMENTAL CORONARY ARTERIOGRAPHY USING ROENTGENOGRAPHIC MAGNIFICATION*

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RECENT efforts to improve the technical quality and thus the diagnostic value of coronary arteriograms have included the use of specially designed timing devices for injection of contrast media^{19, 24-26} specially designed catheters,^{6, 21, 30, 31} aortic and caval occlusion,^{8, 11, 16} temporary asystole,^{1, 3, 10, 15, 18} cineangiography^{20, 21, 30} and direct cannulation of the coronary arteries at open thoracotomy.⁵ Indeed, Portsmann and Kokkalis¹⁸ have stated that "no further improvements are required in the technique of coronary arteriography in dogs." However, the published reproductions of even experimental coronary arteriograms are often incomplete and unsatisfactory, especially with regard to details of fine radi-
cles.^{7, 13, 17, 27} Yet it is essential to have accurate information both experimentally, in evaluating various techniques for improving coronary circulation, and clinically, in assessing coronary occlusive disease.

In an effort to enhance detail in coronary arteriograms, the technique of roentgenographic magnification was utilized. This technique was made possible by the development of roentgenographic tubes with very fine focal spots (0.3 mm. or less) in the past decade. Use of this technique has been limited to the detailed study of bones, joints, soft tissue calcification, and the lung parenchyma. To our knowledge, it has not heretofore been applied to arteriography.

METHOD

Two groups of mongrel dogs weighing between 9 and 18 kg. were anesthetized with pentobarbital and intubated. The

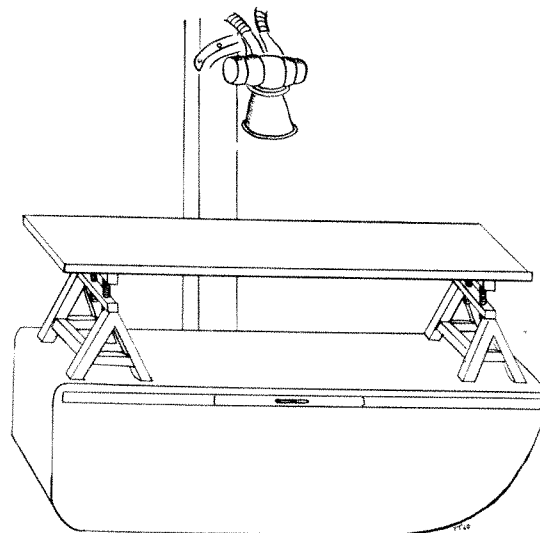


FIG. 1. Diagram of arrangement used to obtain roentgenographic magnification of coronary arteries in the experimental animal (see text).

animals in the first group were placed left side down on a radiolucent table top,* the ends of which rested upon two simple supports placed on either end of an ordinary horizontal roentgenographic table (Fig. 1). Since the height of the supports was adjustable, the distance between the table top on which the animal lay and the roentgenographic table below could be varied. Leads from an electrocardiograph were attached to the animal's limbs. A test film for technique and position was exposed, developed and examined.

The right carotid artery was exposed in the neck of the animal and a large size (No. 9, 10, or 11) N.I.H.† catheter with a curve

* Schönander Elema roll top table.

† U. S. Catheter and Instrument Co., Glen Falls, New York.

* From the Cardiopulmonary Research Laboratory and the Radiology Service, Veterans Administration Hospital, Oteen, North Carolina. This study was supported in part by a grant from the American Heart Association.

near the tip was passed retrograde into the ascending aorta. The curve on the tip of the catheter was maintained in some instances by a stiff, previously curved stylet, which was withdrawn when the catheter tip was in the proper position. When the tip of the catheter was felt to impinge upon the aortic valve, identifiable by vigorous transmitted pulsations, it was pulled back slightly (less than 1 cm.). Fluoroscopy was ordinarily not required for positioning the catheter.

Metacholine chloride* in a concentration of 1 mg./1 cc. of saline solution was placed carefully into the N.I.H. catheter, the total capacity of which was approximately 5 cc., and, when all was in readiness, this was flushed rapidly through the catheter to produce instantaneous temporary asystole. Ordinarily, a dose of 2 mg. of mecholyl was adequate to produce from 20 to 50 seconds of arrest. During asystole, as identified by the electrocardiogram, the animal's lungs were inflated and held still. Then 10 to 15 cc. of 90 per cent hypaque-M was rapidly injected through the catheter, using a hand syringe, after which serial roentgenograms were made. A Gidlund, manually operated, high pressure syringe† was sometimes employed for the injection of radiopaque medium. The catheter was flushed out with heparinized saline while the films were being developed.

In this first group of animals, the 0.3 mm. focal spot of a rotating anode double-focus roentgen-ray tube was used to make the exposures, which were triggered by a foot switch. A simple manual cassette changer consisting of a plywood tunnel and plunger, attached to the roentgenographic table on which the adjustable supports rested, was used to produce multiple exposures. This allowed a choice of arteriograms from which the best could be selected. The target-object distance was adjusted to between 15 and 20 inches, and the object-film distance was set at an equal distance by adjusting the height of the supports upon which the table top holding the animal rested. The

"object" was considered to be a point corresponding to half the thickness of the animal's thorax at the level of the heart. The technical factors were: 20 ma., 62-72 kv., one-half second. No grid was used. Three exposures were made in rapid succession. If technically unsatisfactory arteriograms were obtained due to catheter malposition, or if an additional view was desired, the animal and/or the catheter was repositioned and the procedure was repeated. Otherwise, the catheter was removed and the carotid artery was ligated. After wound closure, the animal was returned to the kennels for recovery from anesthesia and for observation.

The identical procedure was carried out in the second group of animals for comparison, using conventional target-object and target-film distances. These animals served as controls. In half of them, the same manual cassette changer mentioned above was used, with the animal lying directly on the cassette changer. The 1.5 mm. focal spot was employed, with a target-object distance of 40 inches. The technical factors were: 100 ma., 62-72 kv., one-tenth second. No grid was used. In the remaining animals, the Schönander cassette changer was employed, covered with a Lysholm Schönander linear grid. The animal lay on the Elema roll top table which was placed directly on the cassette changer. A 1.5 mm. focal spot, and later a 2.0 mm. focal spot, was employed. The target-film distance was 40 inches. The technical factors were: 300 ma., 62-72 kv., one-tenth second.

Coronary arteriograms in control animals (Fig. 2, *A* and *B*; and 3, *A* and *B*) were enlarged photographically to the same size as the arteriograms made by the roentgenographic magnification technique (Fig. 4) for comparison of detail, contrast, graininess, etc. Wire standards of known diameter were exposed simultaneously in some studies to estimate the diameter of the coronary vessels observed. One set of wires was placed atop the animal's chest near the heart. The other was placed under the animal's chest.

* Mecholyl Chloride, Merck, Sharp & Dohme.

† Westinghouse Electric Corporation.

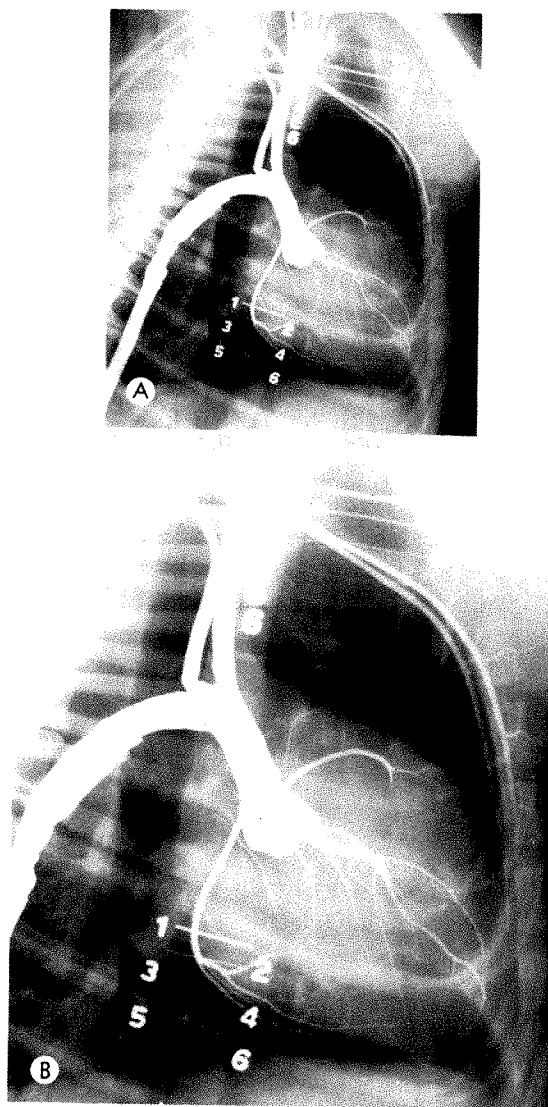


FIG. 2. (A) Coronary arteriogram obtained from a 15 kg. animal using mecholyl arrest and 15 cc. of 90 per cent hypaque injected with a high pressure syringe. The animal was lying directly on a simple manual cassette changer. Steel wire standards were placed on top of the animal's chest (upper group of wires) and under the animal's chest (lower group of wires). The numbers opposite the wires indicate the following wire diameters: (1) 900 μ ; (2) 450 μ ; (3) 300 μ ; (4) 200 μ ; (5) 150 μ ; and (6) 75 μ . Technical factors were: target-film distance 40 inches; 100 ma., one-tenth second, 68 kv., focal spot 1.5 mm., no grid.

Note the irregularity in the upper descending thoracic aorta (near which wire staples of 300 μ diameter are visible) in the thoracic aortic anastomosis. Note also that, although the wires in both

RESULTS

Twenty-one animals were used to obtain 31 coronary arteriograms. In 8 animals in the control group, ten coronary arteriograms using mecholyl asystole were obtained, without using the technique of roentgenographic magnification. In 10 animals, twenty-one coronary arteriograms were obtained using mecholyl asystole and roentgenographic magnification. These arteriograms were twice as large as the arteriograms using ordinary techniques, making possible clear visualization of vessels as small as 100 μ (0.1 mm.) in diameter. This estimate was based upon the known diameter of the wire standards placed above and below the animal's body, and on the diameter of wire staples in the thoracic aorta or superior vena cava of some animals.²⁴ The same detail could not be reproduced by photographic enlargement of arteriograms made by ordinary techniques, even when temporary asystole had been employed (compare Figures 2B and 3B with Figure 4).

COMPLICATIONS

There were no complications attributable to the magnification technique itself. Those inherent in blind catheterization of the ascending aorta, and in producing arrest with mecholyl were the only ones encountered. One animal expired several hours after the procedure, which had required the use of an unusually large dose of mecholyl (10 mg.) as well as succinylcholine chloride (anectine) (10 mg.) to control severe bronchospasm. This animal was the only

sets of standards were exactly the same size, those placed beneath the animal's chest appear to be smaller than those on top of the chest (upper group), since the former were closer to the roentgenographic film.

(B) Same coronary arteriogram as in A, but photographically enlarged approximately 2 \times . Note the increased graininess of the print with no improvement in the detail of the fine vessels, staples, or wire standards. (Compare with Figure 4.)

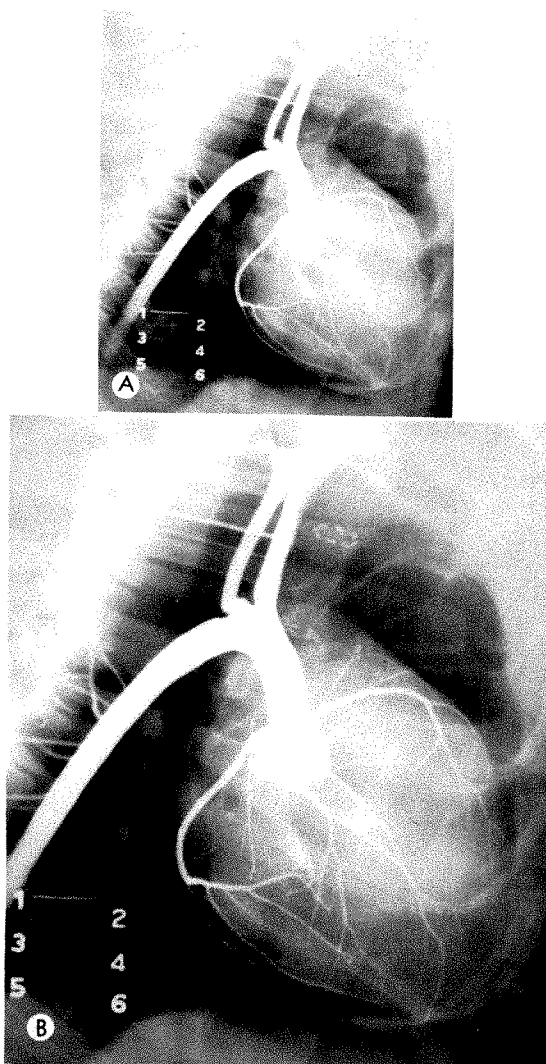


FIG. 3. (A) Coronary arteriogram obtained from an 18 kg. animal using mecholyl arrest and 15 cc. of 90 per cent hypaque injected with a high pressure syringe. The animal was lying on an Elema roll top table placed directly on the Schönander rapid cassette changer. The same wire standards were used as in Figure 2, A and B. Technical factors were: target-film distance 40 inches; 300 ma., one-tenth second, 74 kv., focal spot 2.0 mm., Lysholm Schönander linear grid.

Note the staples of 300 μ wire in two areas anterior to the brachiocephalic artery, representing anastomotic lines of a graft interposed in the superior vena cava.

(B) Same arteriogram as in A, but photographically enlarged approximately 2X. No improvement in the detail of the vessels, staples, or wires can be discerned. (Compare with Figure 4.)

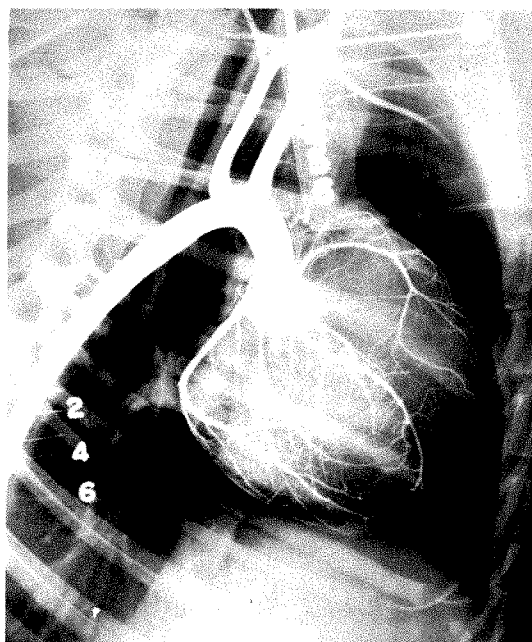


FIG. 4. Coronary arteriogram obtained by the technique of roentgenographic magnification from a 14.5 kg. animal, using mecholyl arrest and 15 cc. of 90 per cent hypaque injected with a high pressure syringe. The animal lay on an Elema roll top table elevated on simple adjustable supports (Fig. 1). A simple manual cassette changer was employed. The same wire standards used in Figures 2 and 3 were placed above and below the animal's chest in the same manner. Technical factors were: 20 ma., one-half second, 74 kv. The 0.3 mm. focal spot was used. The target-object distance was 17 inches and the target-film distance was 34 inches.

Note the 300 μ diameter wire staples of a superior vena caval anastomosis in the area between the ascending aorta and the lead No. 6. Coronary arteries with diameters considerably smaller than 100 μ are clearly visible. (Lead No. 3 in the upper right represents the cassette number.)

one which exhibited disturbing bronchospasm necessitating the use of this drug. This complication was probably due to inaccurate placement of the tip of the catheter. Another animal died when a defective catheter buckled in the left ventricle, with avulsion of the brachiocephalic artery on attempting to withdraw the catheter. A third animal expired following rupture of the subclavian-carotid bifurcation due to intimal dissection of the carotid artery by the catheter. Temporary inver-

sion of the T-waves was observed in most animals following arteriography, with return to a normal pattern within a few minutes after the procedure. There were no instances of generalized convulsions at the time of arrest, and anectine was required only once, as noted above.

DISCUSSION

Wasson²⁹ has been credited with the first demonstration of the technique of magnification of the roentgenographic image with retention of detail. This was reported in 1922. It was achieved with the aid of a 1 mm. pinhole diaphragm, and an 18 inch film-part distance. The method did not gain clinical usefulness apparently until a roentgenographic tube with an ultrafine (0.3 mm.) focal spot was developed in recent years.

Since that time, for delineation of detail in certain core structures (axial skeleton, sella turcica) or for greater clarification of detail in bony lesions of the extremities, it has been repeatedly and amply demonstrated that roentgenographic enlargement by means of a tube with a very fine focal spot is a much more effective and convenient technique than photographic enlargement of a roentgenogram.^{2,4,9,14,22,23,28,33,34} This is especially true of those parts which cannot be brought close to the roentgenographic film because of their central location. Since the heart cannot be in close proximity to the film in lateral and oblique views, the blurring or unsharpness in the original roentgenogram resulting from the penumbra effect of a conventional 1.5 mm. focal spot is merely increased by optical or photographic enlargement. Film grain is also magnified, diminishing clarity. Finally, photographic enlargement entails several additional processes, all of which are eliminated by direct roentgenographic enlargement.

It should be pointed out that Portsmann and Kokkalis¹⁸ mentioned the possibility of using a roentgenographic tube with a fine focal point to delineate fine coronary radicles, but they did not mention the possi-

bility of roentgenographic magnification, which this type of tube makes possible. It appears that the maximum useful enlargement that can be obtained with the 0.3 mm. focal spot is $2\times$;¹² however, Takahaski and others,^{22,23} using a roentgen tube with an autobiasd focal spot of under 0.15 mm., have produced useful magnification up to $4\times$ and $5\times$.

Due to the small size of the fine focal spot, however, the maximum permissible current, at the necessary kv., is 20 ma. Extremely rapid exposure times necessary to stop cardiac motion are thus ruled out. A relatively long exposure time (one-half second) must be used. This makes induced temporary asystole mandatory, if this technique is to be applied to coronary arteriography. No real problem is posed in the experimental animal. Clinically, Arnulf³ and Lehman *et al.*¹⁵ have shown that coronary arteriography using induced temporary asystole is safe and practical. Most workers in this country, however, have preferred not to arrest the diseased or healthy heart, in spite of this evidence.

It is possible that, when significant surgical relief can be offered to patients with coronary heart disease based upon accurate preoperative roentgenographic appraisal of the coronary vessels, the risk of performing coronary arteriography with induced arrest and roentgenographic magnification will be acceptable, if maximal detail is required.

Another minor disadvantage of the method is that the use of fluoroscopy to position the catheter in the ascending aorta is inconvenient. With experience in the animal, the frequency of successful catheterization of the ascending aorta without the aid of fluoroscopy is high. Pressure tracings obtained through the catheter can also be used to guide withdrawal of a catheter which has entered the left ventricle, and thus assist in placing the catheter in the proper position.

The technique of roentgenographic magnification should be useful experimentally and clinically where very fine arterio-

graphic detail is sought. The experimental field of fine vascular anastomoses, and the clinical field of visceral, and especially renal, arteriography suggest themselves as applicable to this technique.

Roentgenographic magnification is very conveniently adapted to cineangiographic techniques. A study of coronary cinearteriography using such a technique will be the subject of a subsequent report.

SUMMARY

The well-known technique of magnification of the roentgen-ray image with the use of a roentgenographic tube with an ultra-fine focal spot, and with target-object and object-film distances approximately equal, has been successfully applied to experimental coronary arteriography. There was much greater clarity of detail and much better contrast than that obtainable by photographic enlargement to a comparable size of arteriograms taken with conventional techniques. Vessels with lumina as small as 100 μ or less could be visualized readily. Other experimental and clinical applications are suggested.

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PERCUTANEOUS ARTERIAL CATHETERIZATION AND ITS APPLICATION

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IN THE American medical literature few papers have appeared dealing with percutaneous arterial catheterization using Seldinger's method. This ingenious, closed technique enables the radiologist himself to carry out the procedure. In addition, obvious improvement in the results is obtained. It is the purpose of this paper to create more interest in and to familiarize the radiologist with its wide range of applications. Technical details, a simplification of the original technique, and its application in 300 examined patients will be discussed. Percutaneous catheterization by advancing a catheter through a needle is well known.⁹ Because this technique requires large needles in order to introduce a catheter of adequate size, arterial puncture becomes difficult and hazardous. As a result, this method has not become popular for roentgenographic procedures, although it is still used for intravenous administration of drugs. In 1953 Seldinger¹¹ described a method of percutaneous arterial catheterization which allowed the introduction of a catheter equal in size to the puncture needle.

PRESENTLY USED TECHNIQUE

Following the preparation and cleansing of the skin, the subcutaneous tissue overlying the artery is infiltrated with a local anesthetic. A 3 mm. "nick" is made through the skin and subcutaneous tissue with a No. 11 knife blade in order to decrease friction of the needle and catheter. An arterial needle is advanced through the subcutaneous tissue, and an attempt is made to feel the pulsating arterial wall with the needle tip. As soon as the artery is located, it is pierced with a jabbing motion. The needle is advanced in the artery to secure a correct intravascular position. A guide wire with a soft flexible tip (stainless

steel, guitar string,⁷ or nylon guide¹¹) is introduced through the needle into the artery. The needle is withdrawn and manual compression is applied at the puncture site, in order to prevent bleeding around the guide. A snugly fitting catheter is threaded over the guide wire through the subcutaneous tissues and arterial wall into the artery.

EQUIPMENT

A. NEEDLE

A correct intraluminal position of the needle in the artery is of paramount importance. Subintimal or subadventitial passage of the stylet is not uncommon unless the needle is advanced in the artery. Experience has shown that intra-arterial advancement of the puncture needle is best accomplished by combining Seldinger's double needle with a blunt obturator. The outer needle is made from Teflon. The antifrictional properties of this semirigid, autoclavable plastic make it an excellent needle material.

The arterial wall is located with the needle tip and punctured with a short "jab." (Fig. 1). Puncture of both arterial walls usually cannot be prevented (A). The sharp stylet of the inner needle is removed and the needle is slowly withdrawn until blood flows freely from the inner wide lumen 18 gauge needle (B). Now the inner needle is removed, and a blunt obturator is

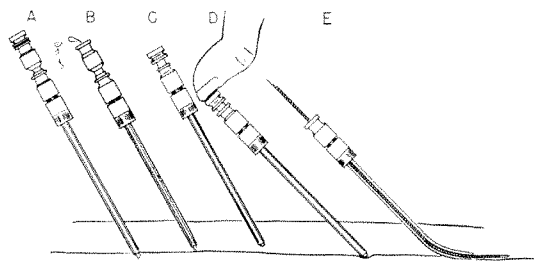


FIG. 1. Technique of arterial puncture.

TABLE I

	Outside Diameter (mm.)	Inside Diameter (mm.)	Injection Pressure	Hypaque 90 Per Cent (cc./sec.)
Radiopaque Catheter (Ödman-Ledin, Yellow)	2.85	1.5	200 lb./in. ²	23
Clear Polyethylene Tubing PX 079	2.82	2.01	200 lb./in. ²	50

introduced extending 1 mm. beyond the Teflon needle (C). At this point the needle can be easily advanced without perforating the wall of the artery. This is best accomplished by pushing gently with the thumb against the hub of the blunt obturator (D). Following the withdrawal of the blunt obturator, the guide wire is easily introduced (E). The described technique of arterial puncture has proved helpful for peripheral arteriography as well, since the possibility of "sheathograms" is almost completely eliminated. With the stylet passing through the Teflon needle (16 gauge), large catheters can be introduced, making the use of larger puncture needles and larger stylets superfluous.

B. CATHETER

For this procedure radiopaque or non-opaque polyethylene tubing may be used. Ödman¹¹ has shown that polyethylene is superior to other catheter materials, since it does not lose its shape at body temperature. Any curvature can be given to the catheter tip by forming it in boiling water.

Radiopaque polyethylene catheters have the obvious advantage of being visible at fluoroscopy. They are, however, thick walled, resulting in much slower flow rates as compared with clear polyethylene tubing. Table I gives the flow rates obtained through a yellow Ödman-Ledin catheter as compared to those with a clear tubing PX 079.* In spite of the slightly larger outside diameter of the opaque catheter, only half as much contrast medium can be injected per unit time. The advantage of radiopacity is offset by the high resistance

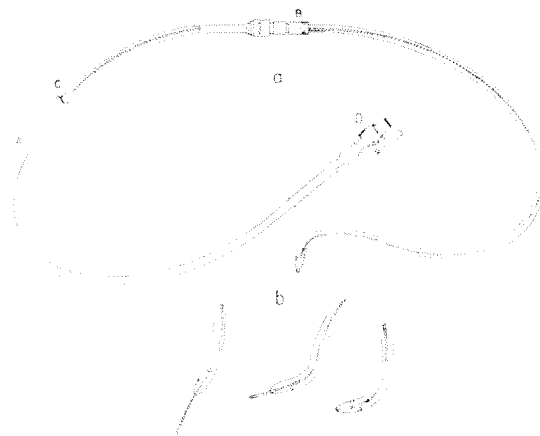


FIG. 2. (a) Diagram showing a simple system which allows fluoroscopic observation of the nonopaque catheter. (b) Diagram showing how a change of extension of the stylet causes straightening of catheter tip.

which makes this type of catheter impractical for aortography and left ventriculography.

Nonopaque polyethylene tubing can be visualized on fluoroscopy by leaving the guide wire in place (Fig. 2a). A semitransparent Teflon tubing (A)† is attached to the catheter by an adaptor (B), allowing observation of the stainless steel guide wire which remains in place during catheterization. The stylet is measured against the length of the catheter and tubing; a piece of umbilical tape (C) is tied about the Teflon tubing to mark this point. The entire system is flushed through a stopcock (D) with heparinized saline solution. By disconnecting temporarily the coupling (B), the stylet can be advanced beyond the catheter tip. By so doing the stiffening wire in the spring stylet tends to straighten the catheter.

* Becton, Dickinson, and Company, Rutherford, New York.

† Franklin X-ray Company, Philadelphia, Pennsylvania.

ter. This is one of the main advantages over standard heart catheters which have a fixed curvature (Fig. 2*b*). Prior to injection the guide wire is removed.

Even large catheters (PE 260 or PX 079) can be introduced with a stylet passing through the described Teflon needle. This is only possible if the catheter tip fits snugly around the guide wire. To make such a catheter, a guide wire is introduced into a piece of polyethylene tubing, and a hemostat is applied to the end of the tubing which is forcefully stretched (Fig. 3). By holding the tip of the stylet firmly with the index finger and thumb of the other hand, it is possible to produce a "snout-like" ending which is cut off with a razor blade at the point of greatest constriction. Several side holes are bored into the catheter tip with a sharp No. 18 or 20 gauge tubing, to minimize the forward jet and consequent recoil during injection.

Heat sterilization is not possible, which is one of the disadvantages of the polyethylene catheters. Ethylene oxide or one of the commercially available liquid germicidal solutions is, therefore, used. The catheters are best sterilized in a straight position in a large plastic or glass tubing. Six hundred catheterizations have been carried out, each with catheters sterilized by Detergicide*, without observing evidence of local or generalized infection.

C. ROENTGENOGRAPHIC EQUIPMENT

For visualization of the abdominal aorta and iliac arteries, for renal and femoral arteriography, and for visualization of the brachycephalic vessels, standard tables with Bucky diaphragms are used. In fact, best roentgenograms are obtained with standard equipment. In cooperative patients a high milliamperage setting with a long exposure time (one-half to one second) results in excellent visualization of large arteries and capillaries on one single roentgenogram. Evaluation of aortic insufficiency or demonstration of coronary arter-

* U. S. Catheter & Inst. Corporation, Glens Falls, New York.

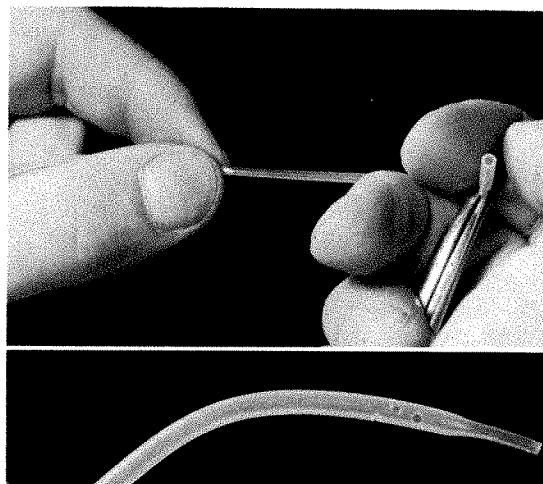


FIG. 3. Photograph showing the stretching of the catheter over the stylet according to the Swedish school.

ies or intracardiac defects requires fast exposures, preferably by a biplane serigraph or cine-equipment.

D. INJECTION APPARATUS

The use of a power injector is mandatory whenever fast injections are required, as for coronary arteriography or visualization of the aortic arch. Most of the other examinations can be carried out by hand if catheters of adequate size are employed. A power injector for low pressure injections (femoral, cerebral, renal, and brachial arteriography) has the advantage of automatic timing, thereby protecting the operator against excessive radiation. The commercially available equipment is bulky and cumbersome in operation which warranted the construction of more versatile injectors.^{5,6}

APPLICATIONS

I. PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

For the vascular surgeon femoral arteriography is probably the most important diagnostic method for evaluation of peripheral arterial disease in the lower extremities. Demonstration and localization of a vascular block in addition to visualization of adequate run-off vessels are of paramount importance. In several cases occlusive

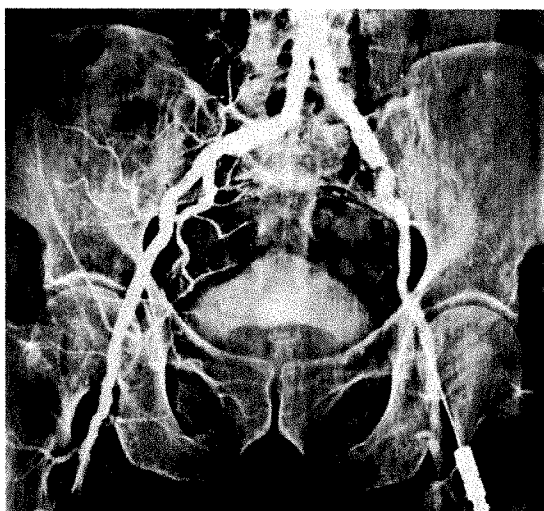


FIG. 4. Severe narrowing of the left iliac artery in a patient with peripheral occlusive disease of both femoral arteries. This was not clinically suspected.

disease of the femoral arteries was associated with narrowing or even thrombosis of the iliac arteries and was not suspected clinically (Fig. 4); therefore, visualization of the iliac arteries has become an integral part of femoral arteriography. In spite of severe generalized atheromatosis, no atheromatous plaques have been dislodged by this procedure in a large group of patients. A small soft catheter (PE 200) should be used, and the iliac artery and abdominal aorta should be gently "explored" with an extremely flexible stylet in which the stiffening wire has been replaced by a cable. If this guide can be passed without resistance into the abdominal aorta, a catheter may be threaded over the guide wire without danger. Even with this very soft stylet, it is sometimes impossible to reach the abdominal aorta either because of the extreme tortuosity of the iliac arteries or because of obstructing plaques at the bifurcation. If the abdominal aorta cannot be reached, an attempt from the other femoral artery is usually successful.

By injecting 20 to 30 cc. of contrast medium through the catheter above the bifurcation, both femoral arteries can be successfully opacified. This technique is

helpful in visualizing severely diseased femoral arteries or grafts which cannot be punctured directly.

2. RENAL ARTERIOGRAPHY

Retrograde percutaneous catheterization is the procedure of choice for visualization of the renal arteries. The obvious advantage over the translumbar approach is the possibility of adequate positioning and re-positioning of the catheter, using small test injections or fluoroscopic control. The ideal renal study is one in which the branches of the celiac axis are not opacified, but the renal arteries are well filled. Since the percutaneous introduction of a catheter requires an open end, a forceful injection tends to opacify the celiac axis and the superior mesenteric artery in spite of numerous sideholes and an ideal position of the catheter at the level of the renals (Fig. 5). Furthermore, the catheter tends to recoil during the injection if higher pressures are used. This difficulty can be partially overcome by the use of the ring catheter, as recently suggested by Williams *et al.*¹⁶ for coronary arteriography. Numerous lateral side holes in the ring direct the jet of contrast medium downward and against the aortic wall where the highest concentration of opaque medium is desirable. An addi-

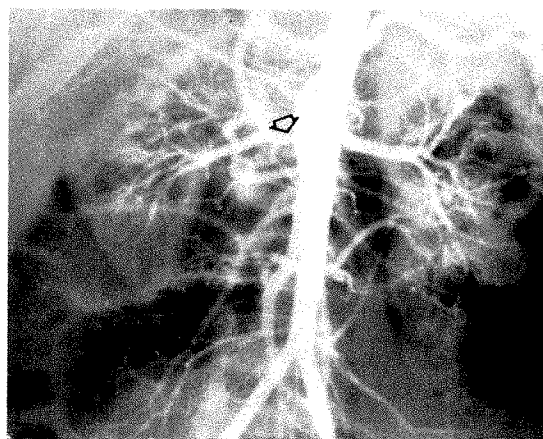


FIG. 5. Renal arteriogram of a two year old patient with hypertension. Area of coarctation of the right renal artery is difficult to identify because of dense filling of other overlying arterial branches.

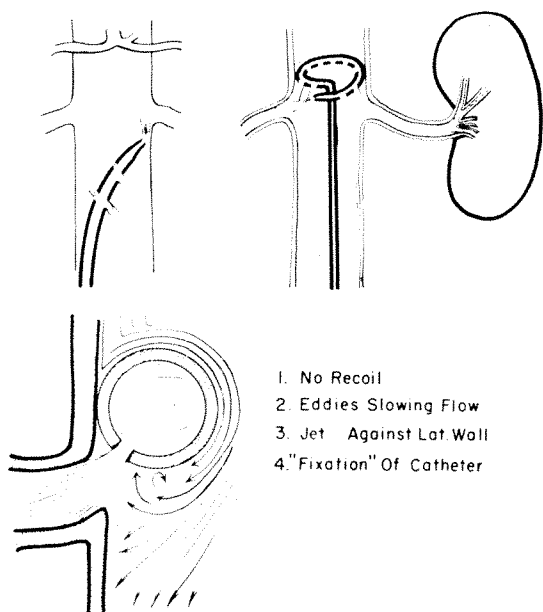


FIG. 6. Diagrams showing some of the advantages of the ring catheter over the standard end-open catheter in renal arteriography.

tional advantage of this catheter is the lack of recoil and self fixation during the injection (Fig. 6). Twenty to thirty cubic centimeters of 50 per cent hypaque are delivered through a catheter (PE 240 or PE 260) by means of a power injector.

In cases where unilateral renal disease is suspected, selective renal arteriography is the procedure of choice.^{8,12,15} The homolateral femoral artery is used for percutaneous catheterization, and a 240 polyethylene catheter with a sharply curved tip is introduced. The guide wire remains in place for fluoroscopic observation of the catheter, which is manipulated close to or selectively into the renal artery. Only 5 cc. of contrast medium is injected under low pressure, and excellent anatomic detail of the renal arterial tree is obtained (Fig. 7). Using this technique the celiac axis, superior mesenteric, or other abdominal branches can be catheterized selectively (Fig. 8, *a* and *b*).

3. CEREBRAL ARTERIOGRAPHY

Visualization of the entire vertebral artery and its intracranial circulation has

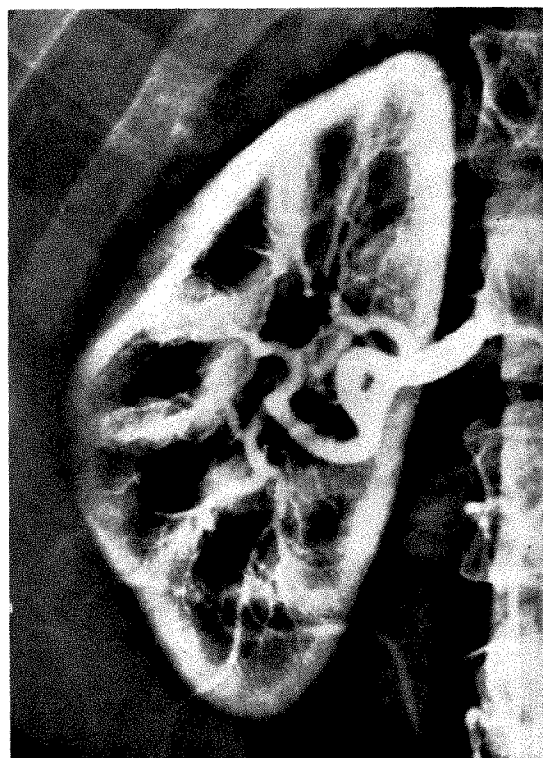


FIG. 7. Normal selective renal arteriogram with good vascular detail.

become of increasing diagnostic importance during the past few years. Direct vertebral puncture will not result in the demonstration of the take-off of the vertebral artery from the subclavian artery, which is of diagnostic importance in older patients with occlusive arterial disease. By catheterizing the brachial artery in the antecubital fossa, a small catheter (PE 200 or PE 205) can be advanced into the subclavian artery to the take-off of the vertebral artery.¹⁰ In younger patients the left vertebral artery can be easily catheterized selectively via the femoral artery.¹³ A straight catheter (PE 205) is introduced into the femoral artery and advanced under fluoroscopic control into the left subclavian and vertebral arteries. Only the left vertebral artery can be entered (Fig. 9, *a* and *b*). In older arteriosclerotic patients with uncoiling of the aorta, the brachial route is to be preferred.

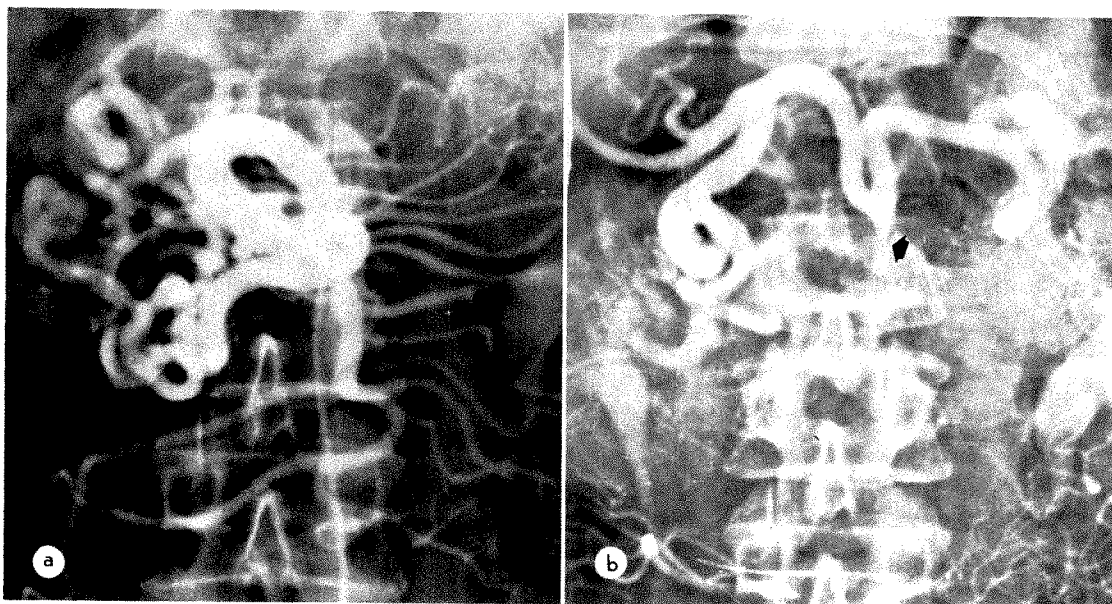


FIG. 8. (*a* and *b*) Arteriograms made with selective injection of the enlarged superior mesenteric artery showing numerous collaterals feeding the common hepatic artery. Note occlusion of the celiac axis (arrow in *b*).

4. THORACIC AORTOGRAPHY

Aortic valvulography has become the most important and most reliable procedure for evaluating aortic insufficiency. Experience has shown that a considerable degree of aortic regurgitation may be present without a murmur.

A large catheter (PE 260 or preferably PX 079) with a curved tip and numerous side holes is used. Ideally, the catheter tip is positioned approximately 1.5 to 2 cm. above the aortic valve plane and a fast injection of 35 to 40 cc. of contrast medium is made with a power injector. The indications for aortography are listed in Table II.

5. CORONARY ARTERIOGRAPHY

Good visualization of the coronary arteries is one of the most difficult angiographic procedures, especially in the presence of coronary arterial disease and consequently decreased flow. Excellent filling of the coronary artery with minute anatomic detail is obtained by selective catheterization. A simpler technique is the use of a ring catheter which allows the delivery of contrast medium close to the origin of the

coronary arteries during systole and diastole.¹⁶ A PX 079 tubing is used and 35 to 45 cc. of contrast medium is introduced by means of a power injector (Fig. 10).

6. LEFT VENTRICULOGRAPHY

One of the most important applications of this technique is for the visualization of

TABLE II
SOME INDICATIONS FOR AORTOGRAPHY

1. Suspected extracardiac left to right shunts (patent ductus arteriosus, aortic pulmonic window, coronary fistula, ruptured sinus of Valsalva, etc.)
2. Evaluation of aortic valvular competence
3. Aortic valvular stenosis
4. Interventricular septal defects with high pulmonary resistance to exclude patent ductus arteriosus
5. Suspected supravalvular aortic stenosis or coarctation
6. Suspected vascular anomalies about the aortic arch
7. Suspected obstructive disease of the brachiocephalic vessels
8. Mitral patients considered for open heart surgery, to exclude associated aortic valvular disease

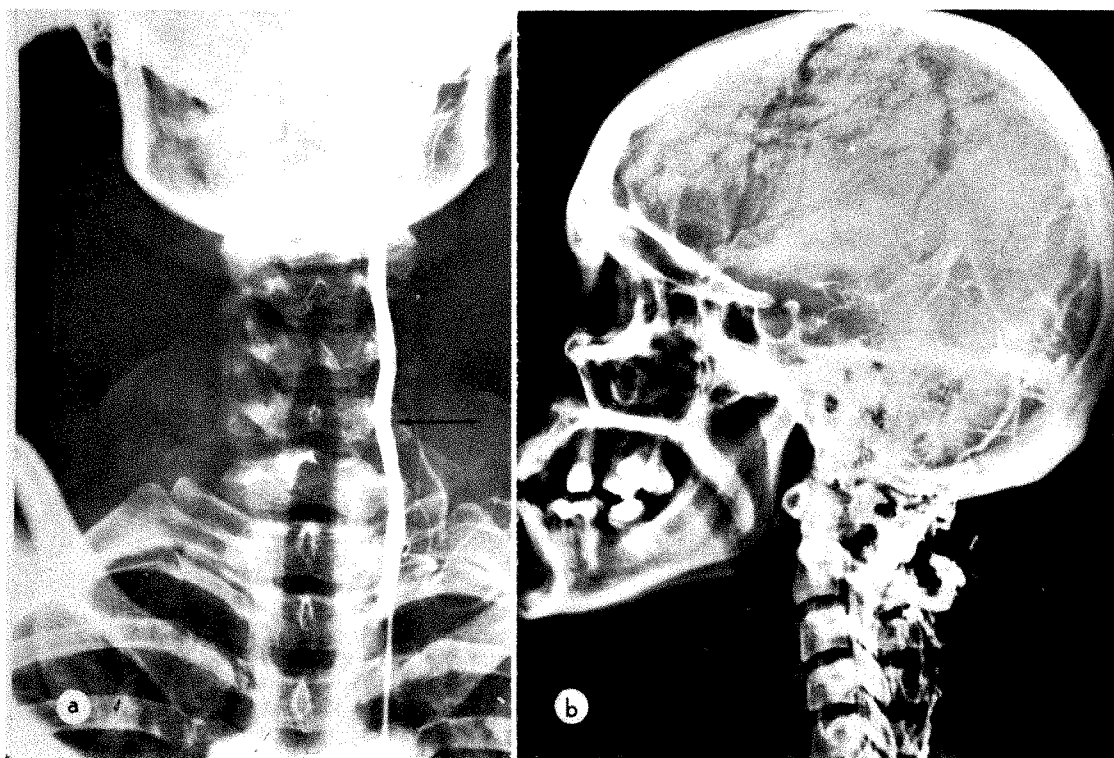


FIG. 9. (*a* and *b*) Arteriograms made with selective catheterization of the left vertebral artery via femoral artery; *b* shows arteriovenous malformation below the foramen magnum.

the left ventricle in acquired and congenital heart disease. The technique and results of this procedure have been reported previously.^{3-5,7} Its indications are listed in Table III. A curved catheter (PX 079 or PE 260) containing a guide wire is passed easily around the aortic arch without entering the brachiocephalic vessels. In the ascending aorta the stylet is extended (Fig. 3) at least 2 cm. beyond the catheter tip so as to eliminate possible damage to the aortic valve leaflets. In 350 successful catheterizations of left ventricles, we have seen no evidence of aortic valve perforation. By increasing the extension of the stylet, the curvature of the catheter can be adapted to the individual case, facilitating passage through the aortic valve. Forty to forty-five cubic centimeters of contrast medium are delivered in less than two seconds with a power injector. For evaluation of mitral heart disease, a slower injection rate is advisable in order to minimize

the occurrence of ventricular extrasystoles and artificially induced mitral regurgitation.³⁻⁵

TABLE III
SOME INDICATIONS FOR LEFT
VENTRICULOGRAPHY

1. Evaluation of mitral competence in acquired and congenital heart disease
2. Evaluation of mitral competence following operative correction of mitral heart disease
3. Suspected subaortic stenosis
4. Small interventricular septal defects with equivocal findings by right heart catheterization
5. Balanced interventricular septal defect not detected by oximetry
6. Patent ductus arteriosus with pulmonary insufficiency or with ventricular septal defects
7. Complex cyanotic heart lesions with increased pulmonary flow
8. Heart disease with mitral insufficiency murmurs with or without history of rheumatic heart disease (Fig. 11).

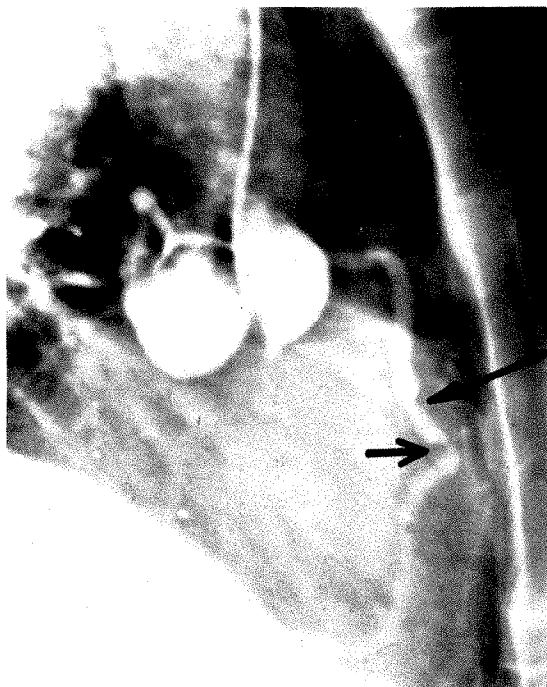


FIG. 10. Coronary arteriogram using a ring catheter in a patient with occlusion of the left coronary artery and a ventricular aneurysm. Because of areas of narrowing in the right coronary artery (arrows), surgery was contraindicated.

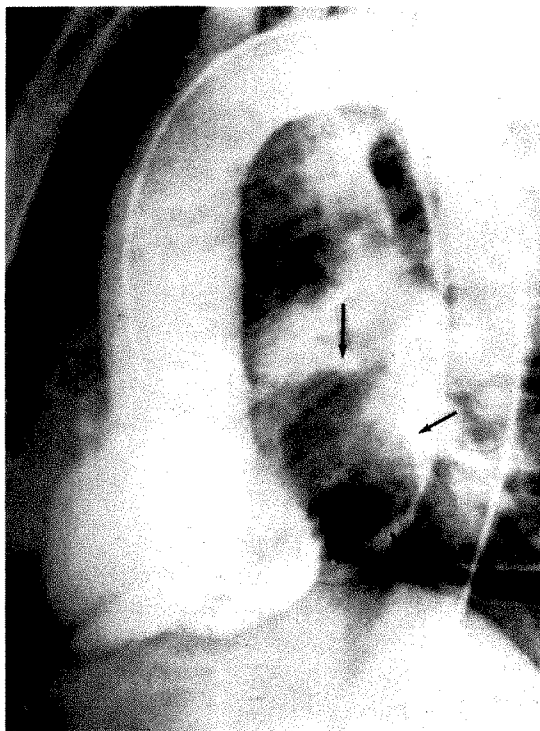


FIG. 11. Patient with a short history of cardiac failure and an unexplained mitral insufficiency murmur. Left ventriculogram demonstrates mitral regurgitation and a large myxoma. (Proved at surgery.)

CATHETERIZATION IN THE PEDIATRIC AGE GROUP

In children below the age of five, a smaller guide wire* passing through a wide lumen 20 gauge needle is used. Percutaneous puncture of the artery may require considerable skill and experience. One of the main difficulties encountered is arterial spasm. A minute amount of sterile mineral oil on the catheter has proved helpful in preventing excessive friction of the catheter during arterial spasm. The youngest children successfully catheterized were two years of age.

COMPLICATIONS

Large series of percutaneous catheterizations have been reported without major complications in the European medical literature.⁸ Our experience consists of 300 cases. The complications occasionally en-

countered are bleeding during catheterization, hematoma following withdrawal of the catheter, and thrombosis of the catheterized artery. The use of a small stylet and relatively large catheter eliminates bleeding around the catheter during catheterization. Following the withdrawal of the catheter, hemostasis is accomplished by manual compression of the puncture site for ten to fifteen minutes. During the first few minutes compression should be intermittently above systolic blood pressure. Slight massaging of the puncture site facilitates hemostasis, which is accomplished chiefly by contraction of the elastic arterial wall. Moderately sized hematomata have occurred in 3 per cent of the examined cases, mostly due to inadequate compression of the puncture site following withdrawal of the catheter. On one occasion a rather large hematoma formed in the pre-peritoneal space with some extension into the scrotum;

* Nedmac, Inc., 708 42nd Ave. N., Minneapolis 12, Minnesota.

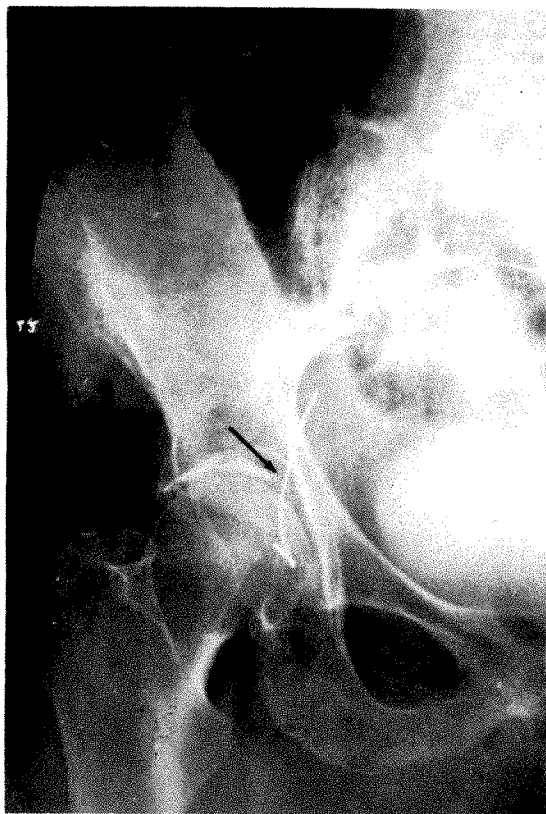


FIG. 12. Tip of broken guide wire lying in adventitia of femoral artery; extravascular passage of the guide wire was due to insufficient advancement of the arterial puncture needle.

it was due to a high puncture of the femoral artery above the ligament, making manual compression of the artery difficult. The hematoma decreased rapidly in size and no further intervention was necessary.

After hemostasis is accomplished, a compression bandage is applied and bed rest for several hours is recommended. Preferably, older patients should be kept overnight in the hospital for observation since bleeding from the puncture site may occur several hours following catheterization.

A more serious complication is the formation of a thrombus at the puncture site. This has occurred in 4 patients, twice in the brachial artery and twice in the femoral artery. In all 4 instances there was marked arterial spasm, making catheterization extremely difficult and also prolonging the procedure. Thrombosis of the brachial artery

is usually of no consequence, since excellent collaterals are present. The other 2 patients with suspected femoral artery thrombosis were observed for several hours in order to exclude the possibility of arterial spasm, which is rather common following catheterization procedures. When the peripheral pulse did not return, the femoral artery was explored by the vascular surgeon, who found a thrombus at the puncture site in both instances. The thrombi were successfully removed and no permanent sequelae ensued.

During catheterization, the catheter should be flushed with heparinized saline solution (4 cc. of heparin per 100 cc. of saline for adult patients). If arterial spasm is present, 2 cc. of procaine or papaverine may be injected prior to withdrawal of the catheter in order to release the spasm.

On one occasion the flexible tip of the guide wire broke off; this occurrence has also been reported by other authors.^{6,15} In this particular instance the guide wire could not be advanced in the artery. Upon withdrawal, it was noted that the flexible tip was missing. An anteroposterior roentgenogram of the pelvis revealed a metallic foreign body in the region of the groin (Fig. 12). On surgical exploration the tip was found superficially in the adventitia of the femoral artery.

Paravascular passage of the guide wire and catheter is not uncommon, especially in older arteriosclerotic patients. Inadequate insertion of the puncture needle is usually the cause. An extravascular passage of the catheter can be recognized immediately since there is no backflow of blood. Usually, there is also mild pain. In patients with severe atheromatosis, an extremely flexible guide wire should be passed gently into the abdominal aorta to serve as a guide for the following catheter; otherwise, the relatively sharp tip of the catheter may engage itself underneath an atheromatous ulcer and extravascular passage may occur. Figure 13 shows such a case where contrast medium was injected into the sheath of the abdominal aorta. In spite of the extensive "sheath-

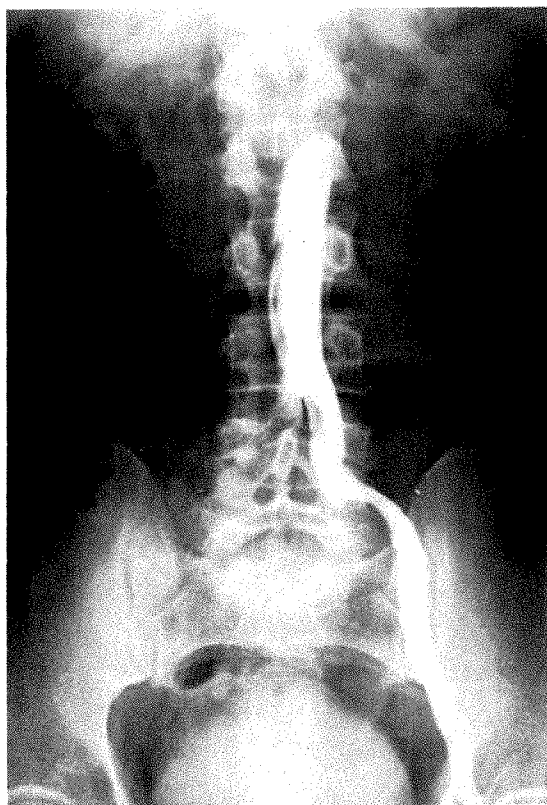


FIG. 13. Arteriogram made with injection of the contrast medium into the aortic sheath in a patient with occlusion of the right iliac artery. In this case the soft guide wire was not advanced into the abdominal aorta, and extravascular passage of the catheter occurred at the bifurcation.

ogram," the patient was operated on the following day and a rather large paravascular hematoma was found. Following surgery, infection ensued which may be in part attributed to the presence of the hematoma.

On several occasions the wall of the left ventricle was partially perforated with the tip of the catheter. This can be readily recognized by a manual test injection under fluoroscopic control using 5 to 10 cc. of 50 per cent hypaque. If a persistent "stain" of contrast medium is visualized, the intramuscular position of the catheter tip is certain. The catheter has to be withdrawn or re-positioned until a free flow of contrast medium is obtained. If this precaution is observed, intramuscular injections with the power injector can be prevented entirely.

DISCUSSION

Percutaneous, arterial, or venous catheterization is a simple technique with a wide range of applicability in different fields of diagnostic radiology. The described introduction of a large catheter by means of a relatively small stylet has advantages over the original technique. Arterial puncture is considered less traumatic to the artery and, furthermore, the bleeding around the catheter during the procedure is minimized. Following withdrawal of the catheter, hemostasis is accomplished more easily. The advantage of radiopaque polyethylene tubing is minimized by its relatively thick wall and consequently restricted flow. By leaving the guide wire in place, nonopaque polyethylene catheters or thin-walled Teflon catheters can be successfully visualized and manipulated under fluoroscopy.

Percutaneous introduction of the catheter is considered to be safer than catheterization by arteriotomy. In a large group of patients, left ventriculography was carried out by surgical exploration of the femoral artery. This was associated with local complications up to 8 per cent, depending on the skill of the operator. So far, the local complication rate of the percutaneous technique is only 1.3 per cent, and no persistent serious complications were observed. The main advantage of the closed technique is the uninterrupted blood flow through the catheterized artery. Consequently, there is no stasis during catheterization, and the formation of a thrombus is a relatively rare occurrence. If arterial spasm is present, a localized thrombus may form and the aid of a vascular surgeon may be required. Since arterial spasm is related to catheter size, this complication is more common if large catheters are introduced.

SUMMARY AND CONCLUSION

1. Arterial or venous percutaneous catheterization is considered to be a safe and useful procedure which is preferably carried out by the radiologist.

2. The procedure has a wide applicability in renal arteriography, abdominal aortography, left ventriculography, thoracic aortography, cerebral angiography, and peripheral angiography.

3. The introduction of an adequately sized catheter is possible by means of a relatively small needle, making arterial cut-downs obsolete.

4. Three hundred patients have been examined, and no major complications have occurred.

5. Percutaneous arterial catheterization should not be regarded as an office procedure since minor complications may occur and surgical assistance may be necessary.

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THE USE OF PERCUTANEOUS TRANSFEMORAL AORTOGRAPHY TO DIAGNOSE ABNORMALITIES OF THE RENAL ARTERIES*

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RENAL arterial and aortic disease is the cause of hypertension in a small but significant percentage of patients with this condition. The diagnosis of hypertension related to reduced renal blood flow and unilateral parenchymal disease is of importance because in many of the cases permanent relief can be effected by operation. Renal aortography is the procedure by which the most accurate evaluation of these patients can be made. Some of the unilateral renal lesions and abnormalities of the aorta and renal artery which are associated with hypertension and a description of the technique of serial renal aortography (the Seldinger technique⁷) and its merits are presented.

TECHNIQUE OF PERCUTANEOUS TRANSFEMORAL AORTOGRAPHY (SELDINGER⁷)

The skin is cleansed and local anesthetic is injected about the common femoral artery. A Seldinger needle (No. 205) is passed through the skin and the femoral artery is punctured. Both walls of the femoral artery are punctured and the stylet is removed. The open end of the needle is then slowly pulled into the femoral artery. As soon as a strong pulsating stream of blood comes out of the needle, the middle part of the needle is removed and the outer cannula (Fig. 1) is pushed approximately 3 cm. proximally into the femoral artery lumen. The unobstructed flow of blood through the needle indicates that the tip of the needle remains in the vessel. When the needle has been passed into the arterial lumen to the level of the guard (4-5 cm.), the stylet is replaced and the polyethylene tube is

prepared for insertion. The guide is a flexible metallic wire which replaces the needle. We have found that the guide needs to be introduced only a few centimeters into the artery before the needle is withdrawn. As the needle is removed, the femoral artery should be compressed to prevent bleeding about the guide until the polyethylene tube (the outer diameter of which is the same as that of the needle) can be threaded over it into the artery. The guide wire is removed when 5 or 6 cm. of the plastic tube lies in the arterial lumen. The polyethylene tube is then pushed up into the abdominal aorta. Any obstruction of it is immediately apparent by cessation of blood flow through the tube. The possibility of dislodgement of atheromatous plaques is reduced by passing only the soft plastic catheter without the guide wire. This is particularly important in patients with clinical evidence of arteriosclerosis affecting the abdominal aorta. To avoid the possibility of penetrating the arterial wall, the semi-rigid guide wire is used only to guide the introduction of the plastic catheter.

The catheter is removed after renal arteriograms are made and pressure is maintained for five minutes over the puncture site. In our experience there has been no instance of hematoma, infection or continued bleeding serious enough to require treatment or prolong the hospital stay despite the fact that all of the patients have had diastolic blood pressure above 100 mm. Hg. The method has been successfully used in children, eleven years and older, without the usual operative exposure of the artery. In small children an open procedure is preferable. The exact position

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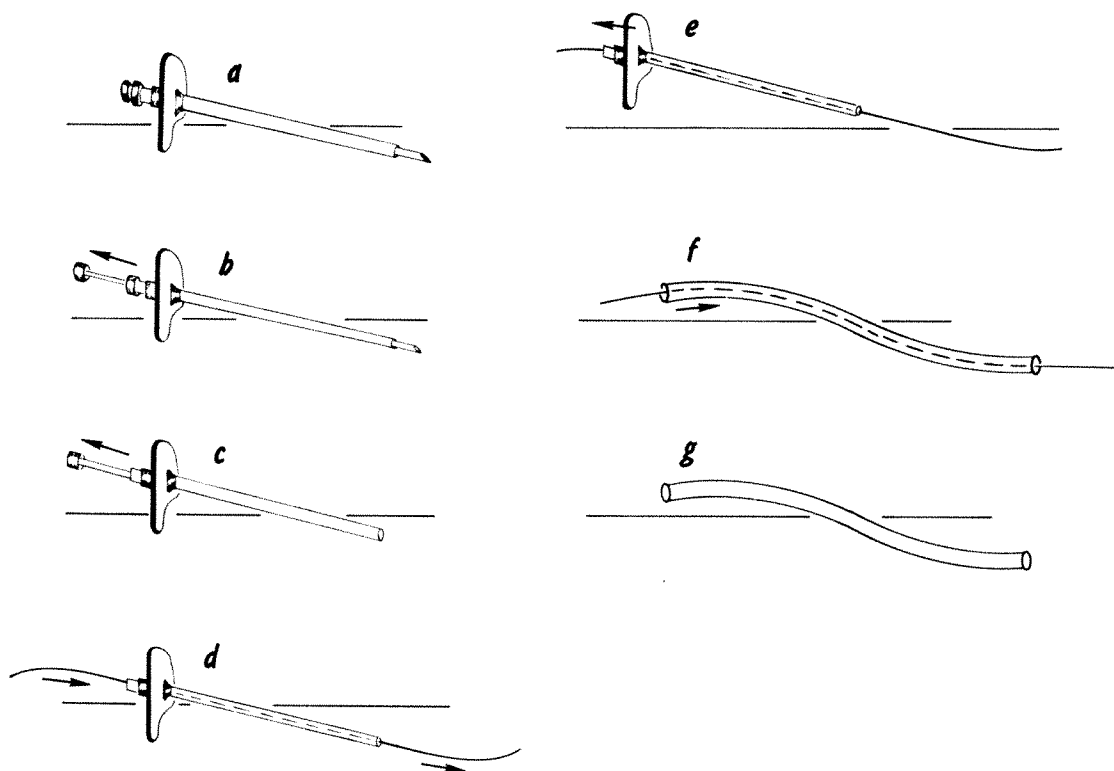


FIG. 1. (a) The Seldinger needle lies within the arterial lumen; (b) the inner stylet is removed to demonstrate flow; (c) the middle needle is removed to allow passage of the smooth surfaced cannula without damage to the arterial intima; (d) the flexible guide is inserted through the cannula; (e) the cannula is removed; (f) the plastic catheter is passed over the guide wire into the artery; (g) the catheter is in place and can be passed into the aorta.

of the tip of the catheter is determined by fluoroscopy after injection of a small amount of the contrast medium.* The tip should be left at the level of the renal arteries. The injected contrast medium also serves as a test dose for hypersensitivity before the main injection is performed. The patient is positioned over the 14×14 inch Schönander film changer loaded with 20 films. The exposure rate is 4 per second for two seconds and 2 per second for six seconds. With this rate the optimal visualization of the visceral arteries is obtained. The arterial and venous phases of the nephrogram are also obtained. Diatrizoate (opaque 50 per cent) was used. The amount

injected varied between 20 and 40 ml., depending upon the size of the patient; as little as 10 ml. is sometimes sufficient. For the injection we have utilized the Gidlund mechanical syringe with the injection pressure of 4 kg./cm.² However, hand injection also produces satisfactory arteriograms if a mechanical device is not desired.

Figures 2 through 9 illustrate the types of abnormalities which can be diagnosed and the value of arteriograms in planning correct therapy.

DISCUSSION

The diagnosis of renal vascular lesions associated with hypertension usually is based on abnormalities revealed by intravenous pyelography, individual renal function studies, urinalysis, and aortography when disease in the renal artery is demon-

* Fluoroscopy is not essential for renal arteriography. The length of the catheter may also be determined by measuring the distance from the groin to the xiphoid process. This will ensure visualization of all abdominal aortic branches.

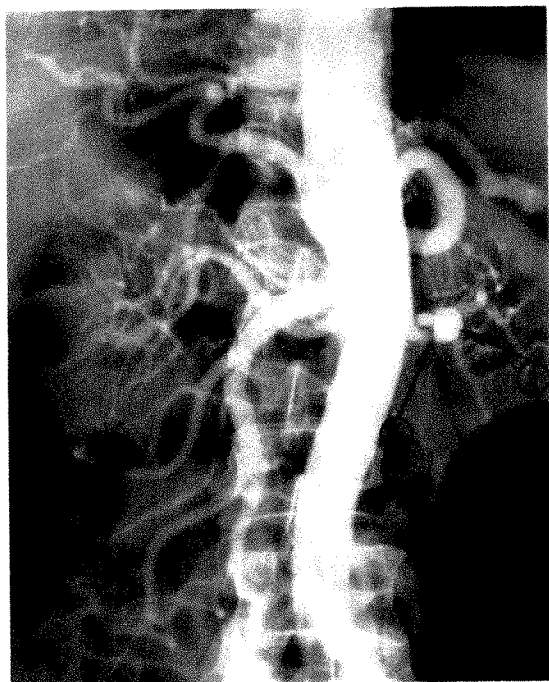


FIG. 2. W. B., male aged 53. The blood pressure of this patient was 240/140 for a duration of one year. Phenolsulfonphthalein excretion was 20 per cent at 15 minutes. Urine catecholamine test was within normal limits and the phentolamine (regitine) test was negative. An intravenous pyelogram showed a decreased density of the left nephrogram. Aortogram shows a stenosis of the left renal artery (1) and a post-stenotic aneurysm (2). Nephrectomy was performed.

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strated. In some instances the diagnosis is suggested by absence of function, or abnor-

malities seen on intravenous pyelograms; however, many patients have normal intravenous pyelograms, and renal function studies by bladder urine are usually normal. Margolin *et al.*⁴ summarized the incidence of abnormal findings on intravenous pyelograms, phenolsulfonphthalein tests, and urinalyses in a collective review and noted wide variations in individual tests. The filtration rate, volume flow per minute, and urine sodium concentration of the kidneys with renal artery diseases are usually lower than in the normal kidney but the osmo-

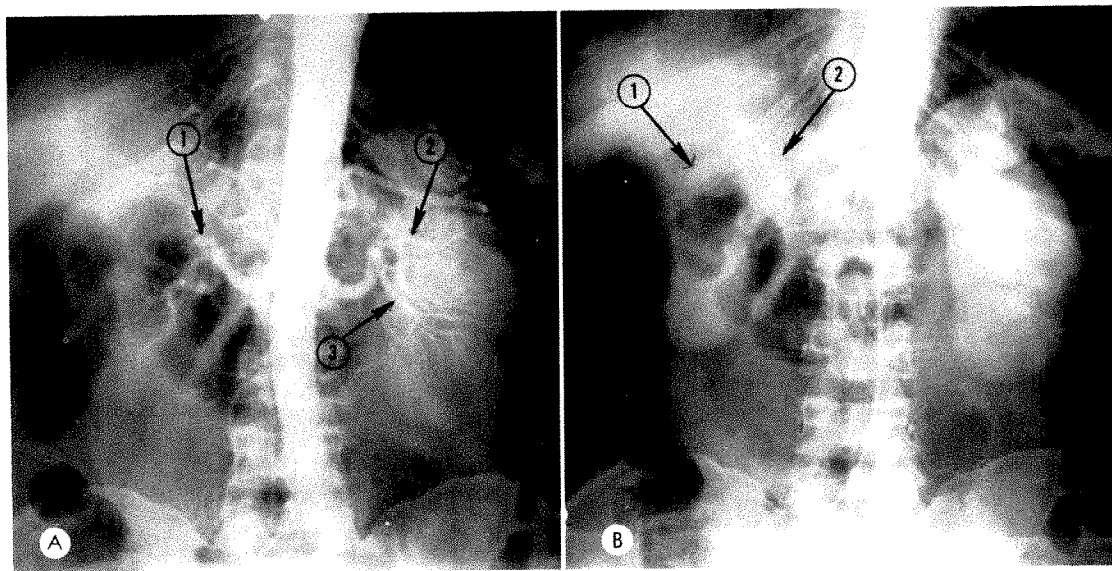
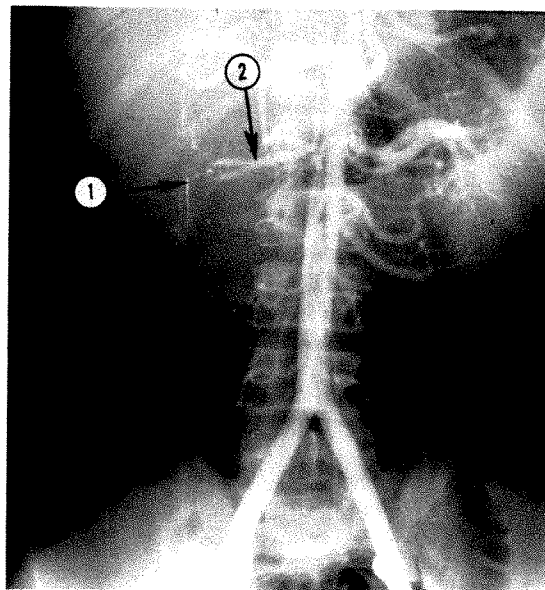


FIG. 3. J. G., male aged 41. The blood pressure of this patient was 220/130 on examination. It was known to be normal five months before hospitalization. Phenolsulfonphthalein excretion at 15 minutes was 23 per cent and the blood urea nitrogen was 10 mg. per cent. An intravenous pyelogram showed a normal excretory system and a right kidney which was slightly smaller than the left. Urine content of catecholamines was within normal limits and the regitine test was negative. (A) Aortogram shows obstruction of the superior branch of the right renal artery (1). The normal superior (2) and inferior (3) branches of the left renal artery are visualized also. (B) The margins (1 and 2) of the atrophic upper pole of the right kidney are seen. Right nephrectomy demonstrated an infarct of the upper half of the right kidney.

FIG. 4. J. L., male aged 14. The blood pressure was discovered to be 170/100 during an examination for athletic participation. The nonprotein nitrogen was 13 mg. per cent. An intravenous pyelogram showed a small right kidney. During cystoscopy prompt excretion of indigo carmine from the right ureter was observed. Aortogram shows the small right vascular nephrogram (1) and the right renal artery (2). The vascular nephrogram of the left kidney demonstrated the compensatory enlargement associated with hypoplasia of the right kidney.



larity may be normal or high.^{3,6} Bilateral renal artery disease or segmental renal infarction may not produce significant differences in individual functional capacities. If the hypertension has existed a sufficient time, the urine of the contralateral kidney may have protein and other abnormal constituents. These considerations are of importance but it is frequently impossible to determine which kidney is primarily affected without performing renal arteriography. Individual renal function

studies are misleading when parallel diminution in function results from aortic coarctation, bilateral renal artery disease, or bilateral parenchymal disease. Unilateral depression of renal function associated with parenchymal disease may be difficult to

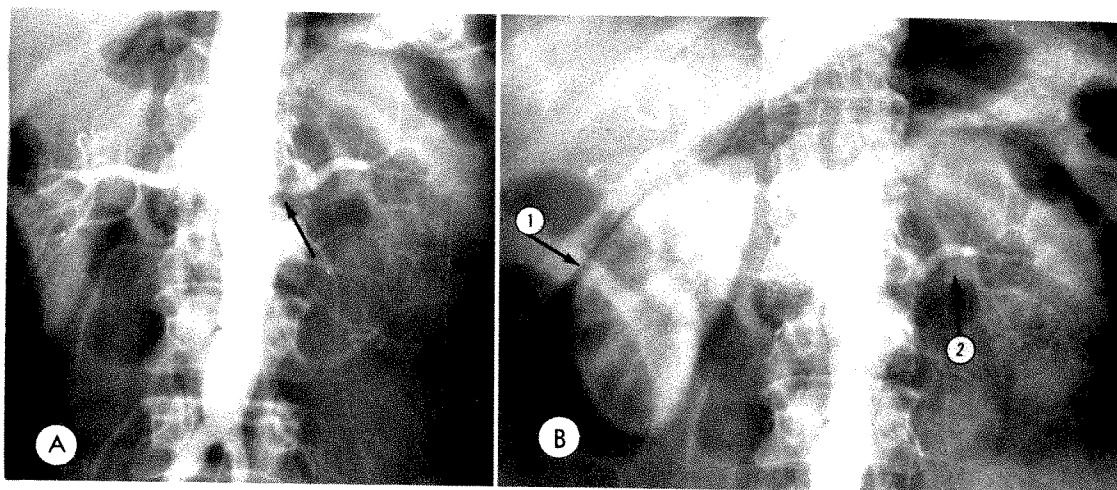


FIG. 5. T. F., male aged 59. The blood pressure of this patient was known to be 160/60 before the onset of severe headaches and syncopal attacks in September, 1959. At this time it was 240/120. Hemorrhages in the fundi were present. The test for catecholamines was within normal limits and there was no change in blood pressure after intravenous regitine. Intravenous pyelograms were not abnormal. (A and B) Two of 30 exposures of serial aortography. A demonstrates the early arterial filling phase (exposure 4). A defect in the column of contrast material in the left renal artery (arrow) indicates a severe narrowing due to an atheromatous plaque. (B) shows the venous nephrogram (exposure 8) of the right normal kidney (1) while the delayed arterial filling (arrow) of the left kidney (2) continues. Hypertension was alleviated by left splenorenal arterial anastomosis without sacrifice of the kidney and the patient has been normotensive for one year.

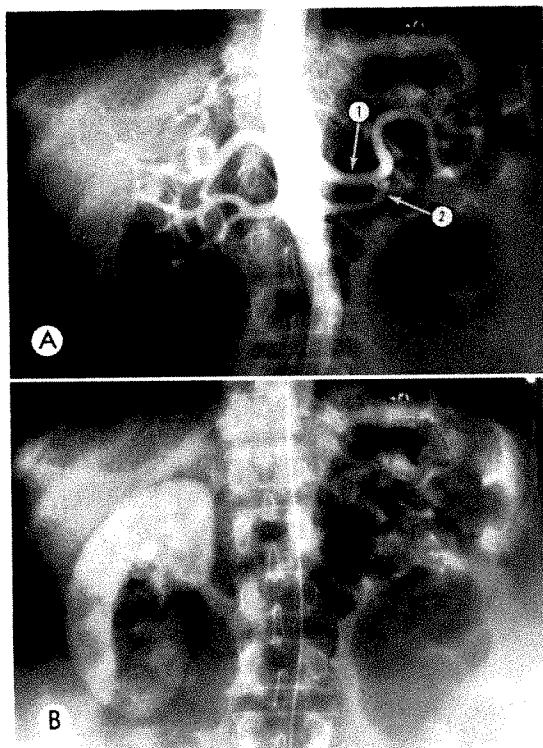


FIG. 6. H. T., female aged 45. This woman had known arterial hypertension (170/110) for three years and had been hospitalized for pyelitis two times in a period of ten years. Intravenous pyelograms showed the left kidney to be slightly smaller than the right. (A) Aortogram shows the splenic artery (1) and the abrupt termination of the left renal artery (2). (B) The right vascular nephrogram (exposure 14) is normal and the left is absent.

distinguish from renal artery disease on the basis of clearance studies, sodium concentration, and osmolarity. Contamination of urine with blood can cause significant errors in urine sodium concentration studies and this test is dependent upon the type of solute load, hydration and other factors. It also requires individual ureteral catheterization with the attendant risk of infection.

Intravenous pyelograms are of assistance if a reduction in the size of the renal nephrogram is demonstrated or the function is

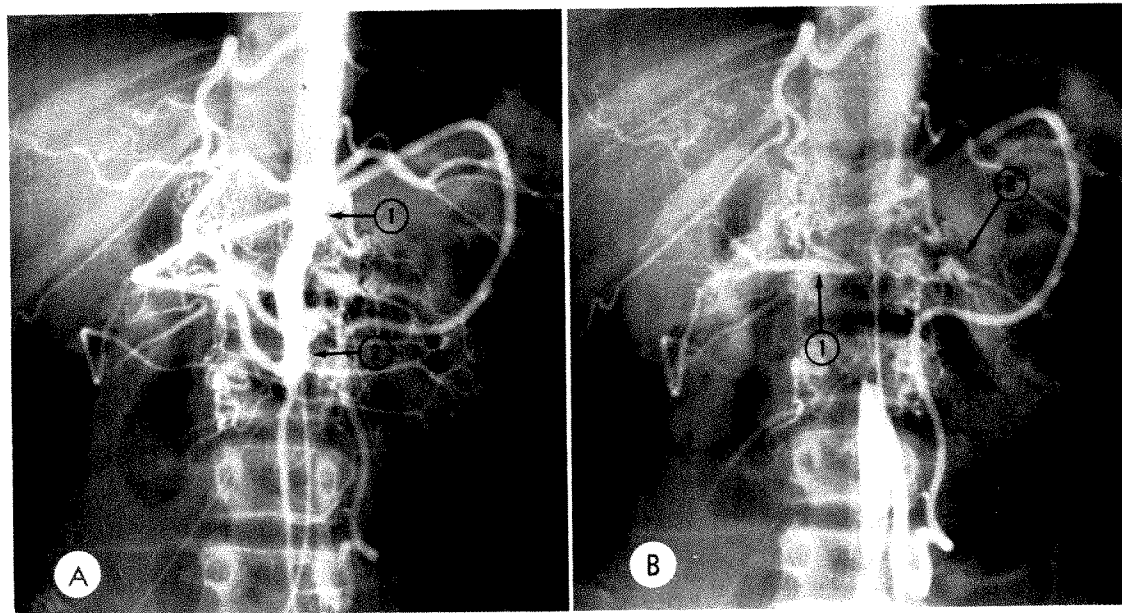
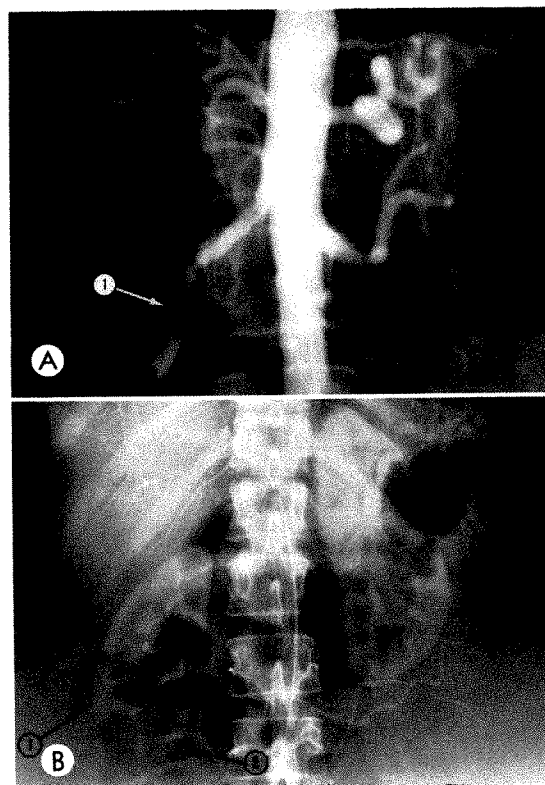


FIG. 7. This child, aged 11, was hospitalized because of the sudden onset of headaches, vomiting and hemiparesis. Papilledema was present and the blood pressure was 240/130. The phentolamine (regitine) test was interpreted as positive and an exploration for pheochromocytoma was performed but no tumor was found. (A) Aortogram demonstrates the cone shaped coarctation of the abdominal aorta (1). A greatly enlarged superior mesenteric artery (2) arises from the narrowed aorta and provides the collateral pathway through the middle colic and the marginal colic artery to the inferior mesenteric artery and the lower

(Continued on facing page)

FIG. 8. J. C., female aged 27. The blood pressure of this patient had been elevated for six years. At the time of examination it was 190/100. An intravenous pyelogram was normal and the phenol-sulfonphthalein excretion was normal. (A) Retrograde aortogram shows the irregular bead-like appearance of the right renal artery (1) due to constrictions in the vessel. The left renal artery (2) is normal. (B) The small vascular nephrogram of the right kidney is seen (1 and 2). The hypertension was relieved by excision of the narrowed segment and primary reconstruction of the renal artery. The right kidney functions normally one year after operation and the patient is normotensive.



greatly reduced, but excretory pyelograms are frequently normal in patients with severe renal artery stenosis (Fig. 8, A and B) or segmental renal infarction. Sometimes the ischemic kidney may produce a nephrogram of greater density than the normal kidney by virtue of its ability to elaborate urine of high osmolarity.^{5,6} This conceivably could lead to the surgical removal of a normal kidney unless arterio-

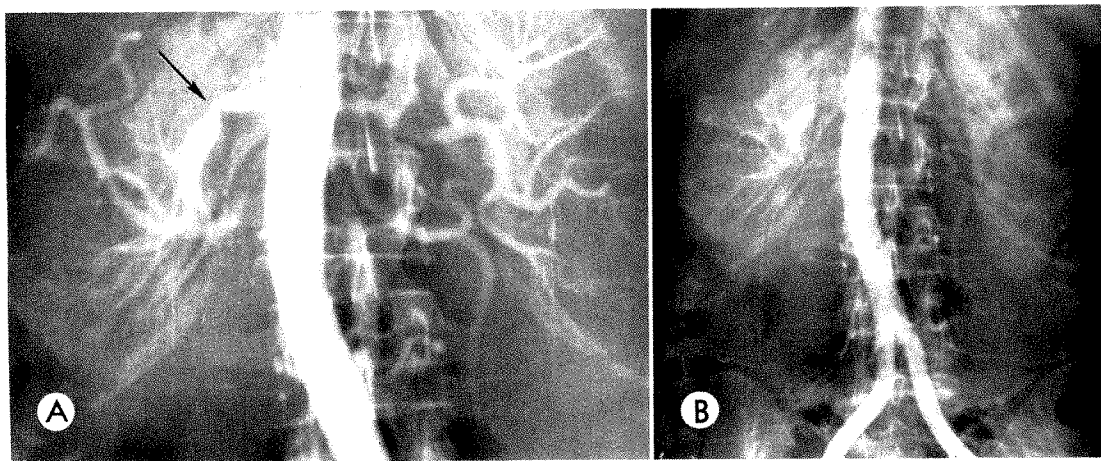


FIG. 9. I. B., female aged 44. Hypertension was noted in this patient six months before hospitalization. The blood pressure was 210/110. The right kidney did not visualize, two hours after intravenous pyelography. (A) Renal arteriogram demonstrates a local constriction (arrow) in the right renal artery. (B) Arteriogram shows delayed arterial filling of the right kidney at the same time that the left kidney shows the venous phase (dissociation pattern). Nephrectomy was performed and the patient has remained normotensive.

abdominal aorta. (B) The left (1) and right (2) renal arteries fill slowly and a slight post-stenotic dilatation is present on the left (1). The lower abdominal aorta is filled by the large inferior mesenteric artery (3). Surgical correction of the coarctation and left renal artery stenosis was performed by homograft bypass to the lower aorta and left renal artery.⁸ The patient has remained normotensive eighteen months after operation. (Reproduced with permission from *Annals of Surgery*.)

graphic studies are performed. Intravenous pyelography is not a dependable quantitative measure of renal function.⁷

The foregoing reasons are sufficient, in themselves, to warrant renal arteriography in every patient before removal of a kidney for unilateral arterial or parenchymal disease is considered. Some occlusive and developmental lesions of the aorta and renal arteries can be corrected without sacrificing a kidney (Fig. 5, *A* and *B*; 7, *A* and *B*; and 8, *A* and *B*); however, aortography is necessary in the accurate delineation of the type and the location of the vascular abnormality in order to institute proper treatment and to conserve the normal kidney.

In this country translumbar aortography has been widely used in the diagnosis of renal artery disease but the complications are significant.⁵ These include principally spinal cord injury, severe renal damage, and acute visceral damage, such as pancreatitis, ischemic necrosis of the intestine, adrenal glands and other organs. Some of the complications of the translumbar approach are associated with the technique and anatomic placement of the needle with relation to the pleura and visceral arteries.⁹ Others are related to the effect of the contrast material in high concentration upon the perfused viscera. A further disadvantage of the translumbar approach is the limitation of the number and technical quality of films obtained by this method. For these reasons we have adopted the Seldinger method of retrograde percutaneous catheterization of the femoral artery to perform arteriography of the renal and other aortic abdominal branches. This method offers the advantage of safety since the catheter lies within the lumen of the aorta and is not as rigid as the translumbar needle. The other complications related to the placement of a needle in the pleural cavity, pancreas and other viscera are completely eliminated. The perfusion of a single major branch of the aorta by high concentration of contrast material is also avoided by placing the catheter just above the (celiac

artery) diaphragm or by using a catheter with multiple holes. The position of the patient affords aortograms of better technical quality and two to six exposures per second can be obtained. This permits visualization of all phases of vascular filling of the kidney and produces excellent nephrograms. The dissociation of the arterial and venous (Fig. 6, *A* and *B*) phase between the affected and normal kidney is of great usefulness in the diagnosis of arterial lesions. The delay in the appearance of the arterial filling phase confirms the reduction of arterial inflow (Fig. 5, *A* and *B*). This procedure has been performed in 100 patients without a serious complication and we believe it deserves wider use in this country for the evaluation of hypertension secondary to unilateral renal disease and vascular abnormalities.

SUMMARY

Renal arteriograms of patients with hypertension associated with renal hypoplasia, coarctation of the abdominal aorta involving the renal arteries, renal artery stenosis, aneurysm of renal artery and segmental renal infarction are presented to demonstrate several types of renal vascular pathology. Although pyelography and individual renal function studies are valuable screening tests in the evaluation of such patients, the diagnosis of lesions amenable to surgical correction must ultimately depend upon renal arteriography. Transfemoral percutaneous aortography is safer, and aortograms technically superior to those using other techniques of renal arteriography are produced.

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HEPATIC ARTERY ANEURYSM*

CASE REPORT

By JAMES L. QUINN, III, M.D.,† and JAMES F. MARTIN, M.D.‡

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ANEURYSM of the hepatic artery is a rare entity. The first reported case was by Wilson¹² in 1819; the first American report was by Jackson³ in 1834. Approximately 129 cases have been recorded in the world literature.^{2,5,11}

The etiology of this lesion is uncertain. It has been found to be associated with a variety of conditions; e.g., trauma, systemic infections, biliary surgery, cholelithiasis, cholecystitis, tuberculosis and polyarteritis nodosa.¹⁰

The antemortem diagnosis has been made with increasing accuracy. Jarvis and Hodes⁴ and Bruwer and Hallenbeck¹ have reviewed the roentgen findings in their cases. Kirklin *et al.*,⁸ Steinberg¹¹ and Jewett⁶ have described the important contribution of angiography in the diagnosis of this lesion before surgery. MacKay and Page⁹ reported on a case in which the diagnosis of an intrahepatic artery aneurysm was made by angiography at the time of exploratory laparotomy.

The prognosis in the untreated state is poor; only 21 have been successfully treated.⁷ This report emphasizes the importance of establishing the diagnosis preoperatively. The following case report illustrates this point.

REPORT OF A CASE

A forty-six year old white male truck driver was admitted to his local hospital in October, 1953. His chief complaints were nausea and vomiting with occasional "midback catches" of six weeks' duration and a 26 pound weight loss during the previous four months. Oral cholecystography and upper gastrointestinal examinations were normal. A rounded calcified cyst-like

structure was seen on the roentgenogram in the right upper quadrant. An exploratory laparotomy was performed at that time with the preoperative diagnosis of pancreatic cyst. A firm lemon size cyst was found in the gastrohepatic ligament closely associated with the common bile duct. Aspiration was unsuccessful. The patient's abdomen was closed without further attempt at removal of the mass. A wound dehiscence developed postoperatively but a satisfactory recovery was made.

He was referred to the North Carolina Baptist Hospital on January 4, 1954 for further evaluation. His only complaint since his previous surgery was intermittent upper abdominal pain. The physical examination revealed moderate tenderness and resistance to palpation in the epigastrium. No masses were palpable. His blood pressure was 118/76 mm. Hg. The hemogram, urinalysis and blood chemistries were normal.

An upper gastrointestinal series revealed a calcified cyst-like structure in the right upper quadrant separate from the stomach and duodenum (Fig. 1 and 2).

Surgical exploration was performed on January 6, 1954 with the preoperative diagnosis of pancreatic cyst. A firm mass, 8 cm. in diameter, non-pulsatile, was found in close association with the common duct and partially surrounded by pancreatic tissue. Sudden massive hemorrhage occurred when the posterior aspect of the mass was being dissected. This was controlled by clamping in the region of the portal vein. The mass was removed and found to contain the hepatic artery which was severed in two places. Ligation was carried out since an end to end anastomosis was impossible. At the end of the procedure no arterial pulsation was felt at the porta hepatis but a large artery was palpable entering the falciform ligament. A T-tube was inserted because of the damage to the common duct.

The gross pathologic diagnosis was saccular

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aneurysm of the hepatic artery. Histologically, there was chronic arteritis characterized by perivascular accumulation of lymphocytes and a fibrous replacement of the muscular coat. Calcification was identified in the vessel wall. The elastic tissue was fragmented and there was a pronounced subendothelial proliferation and distortion of the connective tissue.

Postoperatively, a biliary fistula and partial wound dehiscence developed. The patient gradually deteriorated and died on June 12, 1954. At necropsy minimal biliary cirrhosis and cholangitis were noted. There was complete thrombosis and organization of the hepatic artery and partial occlusion of the portal vein. The immediate cause of death was ascribed to hepatic coma.

DISCUSSION

The case reported emphasizes the need for accurate preoperative diagnosis of hepatic artery aneurysm. The prognosis in the unsuspected and undiagnosed case is very poor.

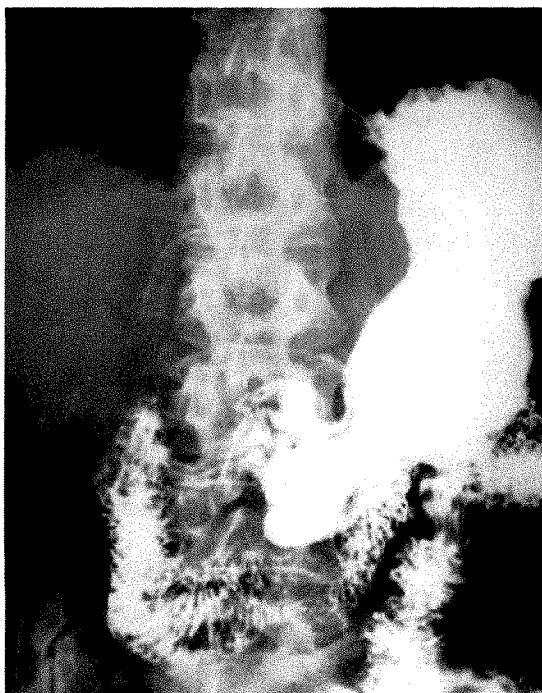


FIG. 1. Posteroanterior recumbent upper gastrointestinal roentgenogram showing a calcified structure to the right of the lumbar spine in the region of the porta hepatis.



FIG. 2. Right lateral recumbent roentgenogram of an upper gastrointestinal study showing a calcified cyst-like structure posterior to and separate from the stomach and duodenum.

The appearance of calcified cystic structures in the right upper quadrant in close proximity to the duodenum and biliary structures should make one consider hepatic artery aneurysm. Angiography is helpful in confirming the diagnosis.

SUMMARY

1. A case of hepatic artery aneurysm is described bringing the total in the world literature to 130.
2. Hepatic artery aneurysm should be considered in the differential diagnosis of calcified cystic masses in the right upper quadrant associated with upper abdominal and upper lumbar back pain.
3. The importance of preoperative diagnosis, which may be aided by angiography, is emphasized.

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UTERINE ARTERIOGRAPHY IN HYDATIDIFORM MOLE*

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SINCE 1952, when Borell and co-workers¹ initiated their studies on uterine arteriography, special attention has been given to uterine tumors, in particular to hydatidiform mole and choriocarcinoma. Later, in 1955, they published reproductions of arteriograms of 2 patients with hydatidiform moles.² Contrast medium filling the intramural cavities was visualized and the authors stated that in their judgment this was a characteristic finding in the disease since it had not been observed in cases of other uterine tumors, pregnancy or post abortion. In 1959, Pescetto and his co-workers³ described arteriograms with a similar finding in 2 patients with hydatidiform moles.

REPORT OF CASES

CASE I (R.N. Hist. No. 273415). This thirty-two year old female was admitted with metrorrhagia of ten days' duration following three months of amenorrhea. The histologic diagnosis on curettage was hydatidiform mole. Ten days after admission, there was a recurrence of the hemorrhage and uterine arteriography was performed (Fig. 1, *A*, *B* and *C*). The arteriograms showed dilated uterine vessels communicating with true intramural cavities which were opacified with contrast medium. Because of this finding, curettage was repeated and residue of a hydatidiform mole was found.

One month later, the patient was re-admitted for metrorrhagia and another uterine arteriography was done (Fig. 2, *A*, *B* and *C*). The arteriograms were identical in appearance to those previously made. Curettage again revealed the remnants of a hydatidiform mole. Her postoperative course was normal without metrorrhagia and the Galli Mainini qualitative reaction test was continually negative after this second episode.

Comment. In this case histologic examination of the curettage scrapings confirmed each time the arteriographic diagnosis of a hydatidiform mole.

CASE II (J.C. Hist. No. 287143). This forty-eight year old female was admitted to the Gynecology Service following abortion of a histologically proved hydatidiform mole pregnancy. Uterine arteriograms (Fig. 3, *A*, *B* and *C*) demonstrated a slightly dilated left uterine artery, normal intramural vessels and an absence of intraparietal blood sacs. On curettage no hydatidiform mole residuum was found. The Galli Mainini qualitative reaction test made fifteen days later was negative.

Comment. In this case the characteristic pattern of a hydatidiform mole was not visualized on arteriograms. No evidence of hydatidiform mole was found on histologic examination at the curettage.

DISCUSSION

Borell *et al.*,^{1,2} after analyzing their cases of hydatidiform mole, came to the conclusions that (1) uterine arteriography is of value in the diagnosis of hydatidiform mole and that (2) this procedure is of importance in patients who have had hydatidiform moles to determine if there is any residuum.

In accordance with our findings, the diagnostic value of uterine arteriography has been proved. Its usefulness in establishing the diagnosis of molar residue was confirmed by histologic examination. Case I showed that each time the true cavities were filled with contrast medium, histologic examination verified the presence of hydatidiform mole residue. On the other hand in Case II the characteristic finding of

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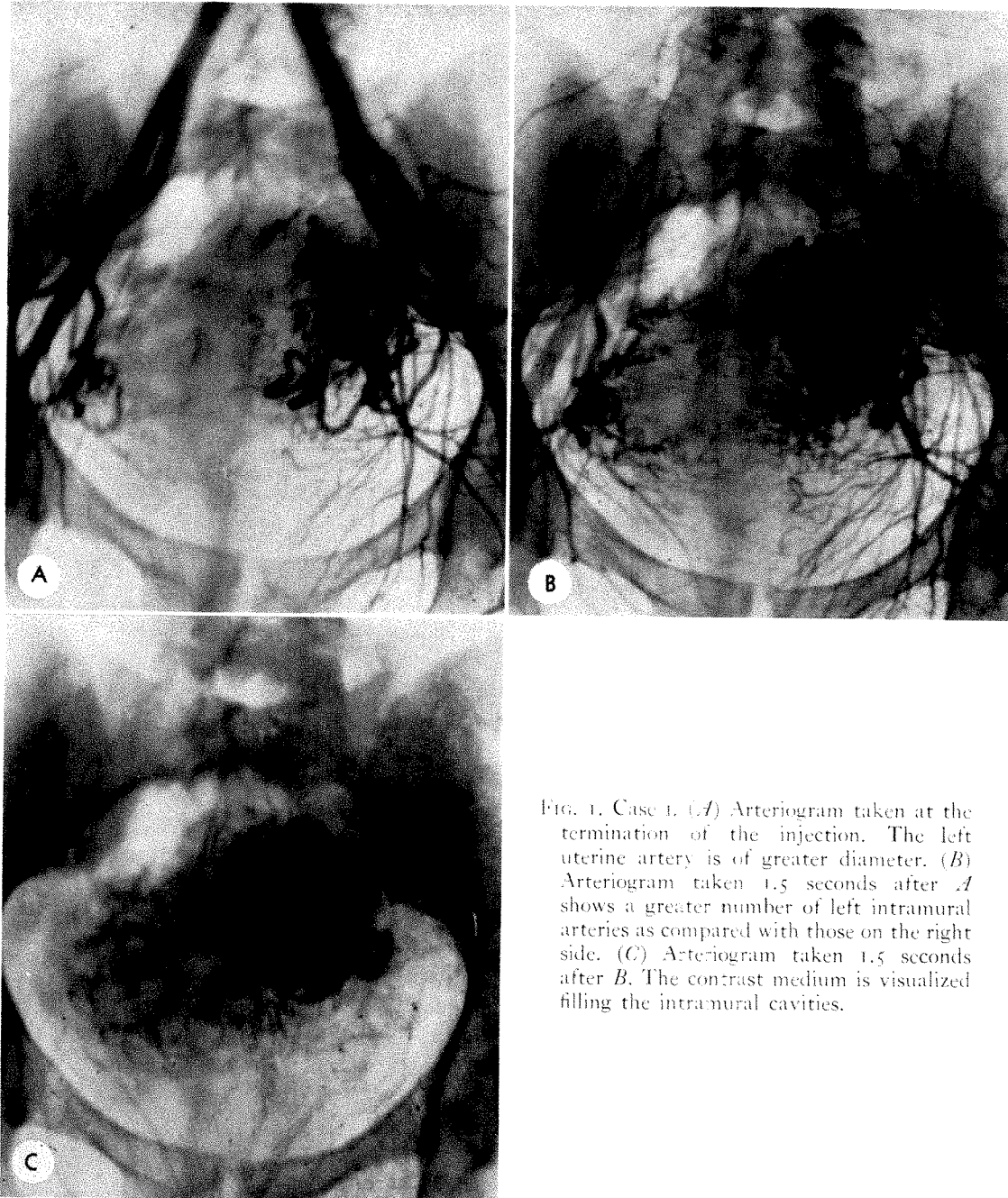


FIG. 1. Case 1. (A) Arteriogram taken at the termination of the injection. The left uterine artery is of greater diameter. (B) Arteriogram taken 1.5 seconds after A shows a greater number of left intramural arteries as compared with those on the right side. (C) Arteriogram taken 1.5 seconds after B. The contrast medium is visualized filling the intramural cavities.

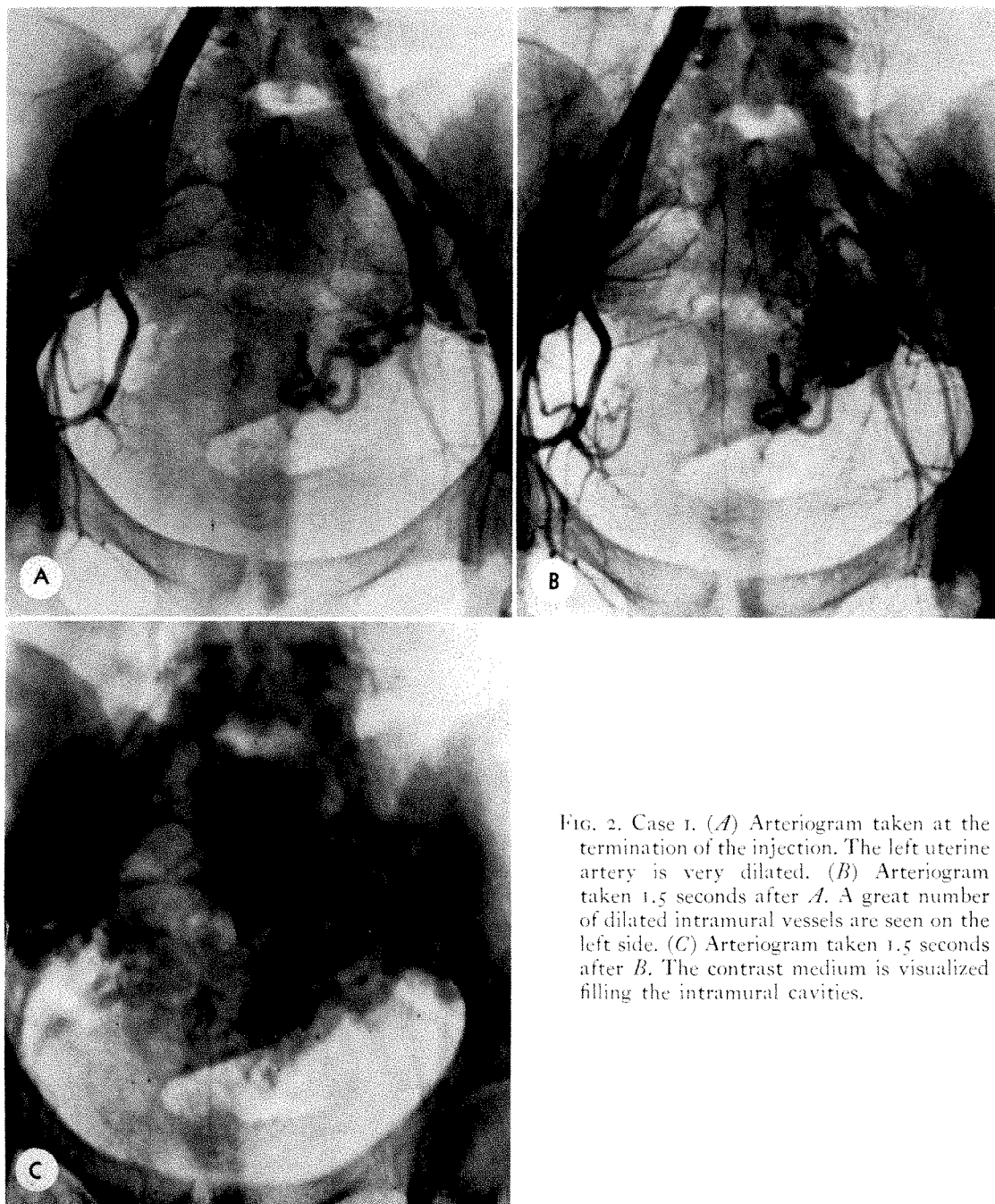


FIG. 2. Case 1. (A) Arteriogram taken at the termination of the injection. The left uterine artery is very dilated. (B) Arteriogram taken 1.5 seconds after A. A great number of dilated intramural vessels are seen on the left side. (C) Arteriogram taken 1.5 seconds after B. The contrast medium is visualized filling the intramural cavities.

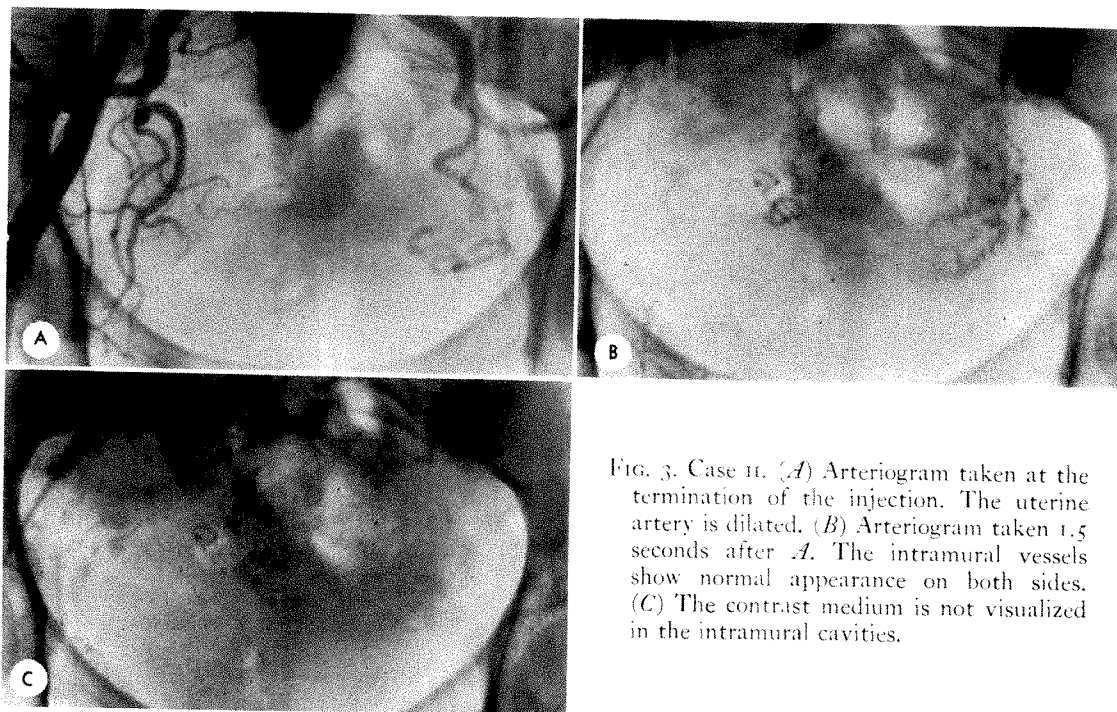


FIG. 3. Case II. (A) Arteriogram taken at the termination of the injection. The uterine artery is dilated. (B) Arteriogram taken 1.5 seconds after A. The intramural vessels show normal appearance on both sides. (C) The contrast medium is not visualized in the intramural cavities.

contrast material in the intramural cavities was not visualized on arteriograms and no remnants of a hydatidiform mole were found on curettage.

SUMMARY

Uterine arteriograms are presented of 2 cases of hydatidiform moles. The histologic examination confirmed the value of this procedure in the diagnosis of hydatidiform moles or in diagnosing the presence of molar residuum.

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AN APPROACH TO FEMORAL ARTERIOGRAPHY

A LONG FILM CHANGER

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A PRINCIPAL objective of femoral arteriography is the discovery of a localized occlusion in a patient with minimal diffuse arteriosclerosis and with patent arteries distal to the occlusion. In my opinion, visualization of arteries distal to the occlusion is the major problem in femoral arteriography. That an occlusion exists can usually be determined clinically. An arteriogram that demonstrates only the proximal end of an occlusive process contributes very little helpful information. The prime objective should be the evaluation of the arteries distal to the occlusive site if at all possible to demonstrate them. The long film changer to be described is an aid in this direction and hence in the selection of patients for surgical correction of femoral occlusive disease.

positioned over the middle one-third of the changer. The side thirds (A and B) of the changer are lead protected. The cassettes are placed all the way in the side slot (C). After the first exposure of one-half of each cassette (D and E), the drive bar (F) shifts the cassettes 7 inches crosswise and a second exposure occurs. We obtain two views, each 7×36 inches, as illustrated in Figure 3, A and B. There is of necessity a one and five-eighths inches space between the upper and lower films. This compromise has not been found a problem. The programming is

LONG FILM CHANGER

Figure 1 is a photograph of the apparatus. It measures 44×24×5 inches and weighs 58 lb. The changer is used on a therapy couch with the couch pad doubled under the upper half of the patient. It is loaded with two 14×17 inch grid cassettes. The changer is activated by the Shipps automatic injector¹ and the changer in turn programs the roentgenographic machine. In the schematic drawings (Fig. 2) one sees a top view and a sectional view of the apparatus. The patient's lower extremity is

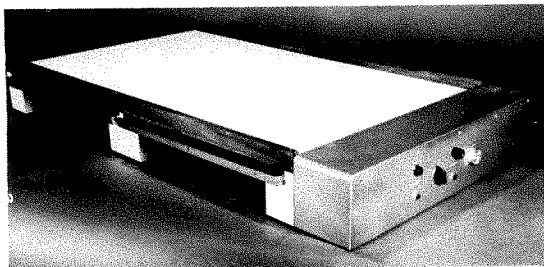


FIG. 1. Long film changer.

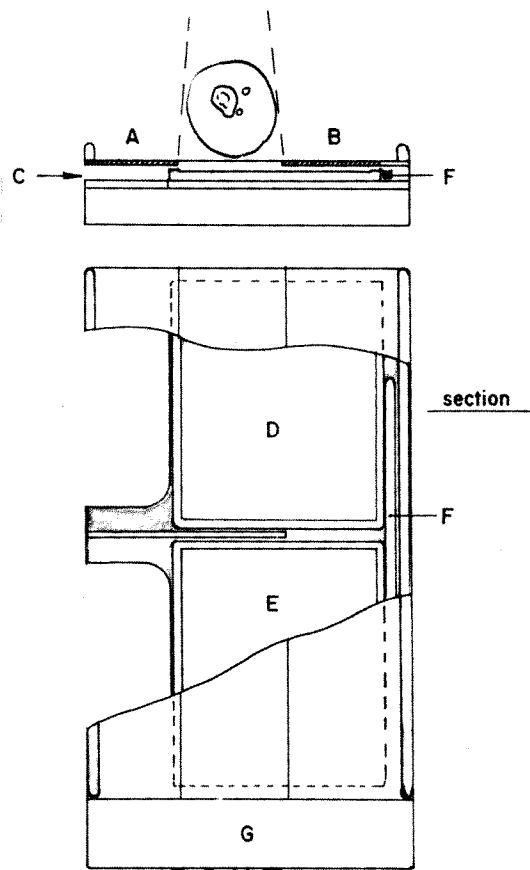


FIG. 2. Schematic drawings.

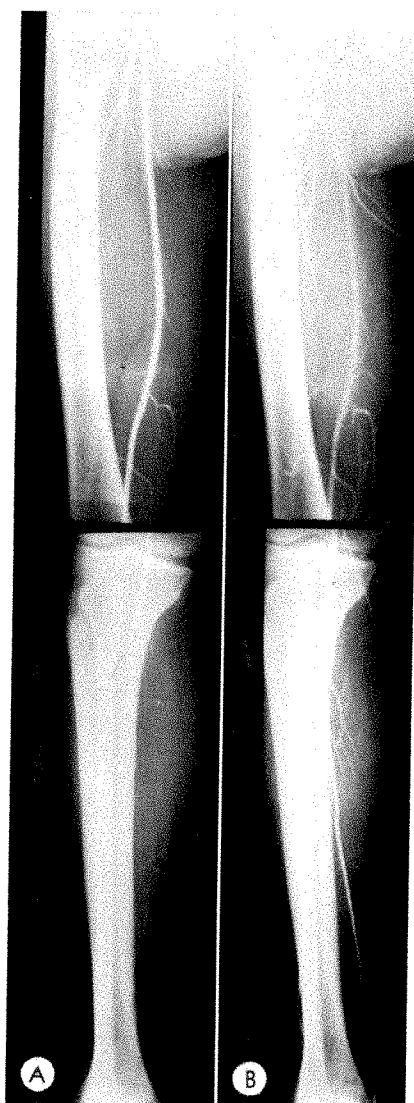


FIG. 3. Percutaneous femoral arteriograms. (A) First exposure at end of injection not showing major arteries distal to the knee. (B) Second exposure (set at two seconds after initial exposure) showing completely the distal vessels.

set in advance so that after the initial exposure there is a choice of one of three delays for the second exposure. The second exposure can be set at two, four or six seconds.

A balanced technique for the thigh and leg is obtained by using high speed screens in the upper 8 to 1 grid cassette (D) and par speed screens in the lower grid cassette (E). The bottom screen of cassette (E) is shielded out by a sheet of black paper

between the screen and film. A tube-film distance of 60 inches is required for coverage.

METHOD OF USE

Patients with a Femoral Pulse. The patient is positioned supine. A percutaneous needle is placed and injection is accomplished using the Shipps injector at low pressure (50 p.s.i. hydraulic pressure) with 30 cc. of 50 per cent hypaque. This requires four to five seconds. At the end of the injection the injector activates the long film changer cycling mechanism (G) and the first roentgen exposure takes place (Fig. 3A). The choice of the time for the second exposure has evolved empirically. If the patient has femoral, popliteal and dorsal pedal pulses we select two seconds (Fig. 3B). If the dorsal pedal is absent we use four seconds, and if the popliteal is absent we use six seconds for the second exposure.

Patients without a Femoral Pulse. If the femoral pulse is good on the opposite side, a retrograde catheter may be employed, or as a second choice the patient may be positioned prone and a low percutaneous abdominal aortic approach used. A tourniquet above arterial pressure is placed on the nonexamined leg in either technique. The dose of 50 per cent hypaque is increased to 50 cc. We use 150 p.s.i. hydraulic pressure through an aortic needle and the delay timer of the injector is set at two seconds to delay the first exposure. The second exposure is set at six seconds. If a retrograde catheter is used, the hydraulic pressure may be higher, depending on the specific flow rate characteristic of the catheter. By precise positioning and the above techniques, one may also use the device for aortofemoral arteriography.

SUMMARY

An automatic long film changer and its use in femoral arteriography have been described. It is possible to obtain 2 roentgenograms 7×36 inches long, with the second exposure at two, four or six seconds after the first exposure. With this unit we

have gained improved preoperative arteriographic information. We feel that evaluation of the arteries distal to the occlusion is of prime importance in femoral arteriography.

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THE JET SIGN IN THE ANGIOCARDIOGRAPHIC DIAGNOSIS OF ANOMALOUS PULMONARY VENOUS DRAINAGE*

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THE diagnosis of anomalous pulmonary venous drainage is no longer of academic interest now that surgical correction of the lesion is feasible. Indeed, in the repair of atrial septal defects, the type of operative approach depends upon the presence or absence of transposed pulmonary veins. Accordingly, refinement in diagnosis of anomalous pulmonary venous insertions is important.

Conventional roentgenography, angiocardiology and cardiac catheterization have significant roles in the diagnosis of transposed pulmonary veins.¹² In the angiogram there is a distinctive "jet sign" at the site of insertion of the anomalous pulmonary veins caused by turbulence of the contrast substance by the unopacified blood from the pulmonary vein. This paper is concerned with evaluation of the jet sign in the diagnosis of anomalous pulmonary venous drainage.

METHOD AND MATERIAL

Angiocardiology with an exposure rate of 2-3 films per second was done using the intravenous route.^{2,10} The erect position was employed in adults; infants and children were recumbent. General anesthesia was rarely used because adults did not require it and small infants usually were mobilized effectively. Exposures of 1/120 sec. were made for infants; while in children and adults they varied between 1/10 and 1/60 sec. Studies were made in frontal and lateral views with only a short interval between the two. The dosage of contrast material (urokon, 70 per cent and hypaque, 90 per cent) was 1 cc./kg. in infants and

children; in adults the dose was 50 cc.

All patients had had complete clinical and laboratory evaluations which included conventional roentgenoscopic, roentgenographic and electrocardiographic studies. All except 4 patients, in 2 of whom the diagnosis was subsequently proved at autopsy, had right heart catheterization which in most instances included dye dilution studies. A total of 19 cases form the basis of this study. Five patients with the jet sign due to anomalous pulmonary venous drainage were reported previously;¹² 14 are new (Table 1).

PARTIAL ANOMALOUS INSERTIONS OF PULMONARY VEINS

Superior Vena Cava. Two patients (Cases 1 and 2, Table 1) were found to have partial drainage of some of the pulmonary veins into the superior vena cava. In Case 1, there was enlargement of the heart and plethoric lung fields consistent with an atrial septal defect. Angiocardiology showed a filling defect along the lateral and posterior aspect of the midportion of the superior vena cava. This defect was present in all the angiograms showing opacification of the superior vena cava during a period of 3 seconds. The diagnosis of anomalous pulmonary venous connection was clearly established by passing a catheter from the superior vena cava into the right superior pulmonary vein.

The other patient in this group was an asymptomatic nurse who, on roentgen examination of the chest, was found to have a mass in the right upper hilus (Fig. 1A). Angiocardiology (Fig. 1B) disclosed a

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TABLE I
JET SIGN IN ANOMALOUS PULMONARY VENOUS DRAINAGE

	Case No.	Age (yr.)	Sex	Associated Defects	Confirmed by
Partial Insertion of Pulmonary Veins into:					
Superior Vena Cava	1	42	F	Atrial septal defect	Cardiac catheterization
	2 (Fig. 1)	34	F	None	Unproved
Junction of Superior Vena Cava and Right Atrium	3 (Fig. 2)	36	F	Atrial septal defect and congenital mitral stenosis	Cardiac catheterization, operation, autopsy
	4 (Fig. 3)	26	F	Atrial septal defect; mild pulmonary stenosis	Cardiac catheterization
	5 (Fig. 4)	48	F	Atrial septal defect and left superior vena cava	Cardiac catheterization
Right Atrium	6*	14	M	Atrial septal defect and pulmonary stenosis	Cardiac catheterization
	7 (Fig. 5)	29	F	Atrial septal defect	Cardiac catheterization, operation
Left Innominate Vein	8 (Fig. 6)	31	M	Anomalous left superior pulmonary vein	Cardiac catheterization
	9	4	M	Anomalous left superior pulmonary vein	Cardiac catheterization
	10 (Fig. 7)	48	M	Heart failure and old myocardial infarction	Cardiac catheterization
	11*	29	M	Rheumatic mitral stenosis; all left pulmonary veins anomalous	Cardiac catheterization, operation
Total Insertion of Pulmonary Veins into:					
Junction of Superior Vena Cava and Right Atrium	12*	16	F	Atrial septal defect	Cardiac catheterization, operation
Right Atrium	13*	28	M	Atrial septal defect; mild pulmonary stenosis	Cardiac catheterization
	14 (Fig. 8)	8	F	Atrial septal defect	Cardiac catheterization
Left Innominate Vein	15*	42	F	Atrial septal defect	Cardiac catheterization, autopsy (1957)
	16 (Fig. 9)	2 mo.	F	Atrial septal defect	Autopsy
Coronary Sinus	17 (Fig. 10)	8 mo.	M	Atrial septal defect	Autopsy (Fig. 10E)
	18	3	M	Atrial septal defect	Cardiac catheterization, autopsy
	19	4 mo.	M	Atrial septal defect	Cardiac catheterization, autopsy

* Previously reported.¹²

large filling defect in the lateral aspect of the midportion of the superior vena cava. The defect was visualized in the entire series of angiocardiograms made during a period of 8 seconds; confirmation of the diagnosis of anomalous pulmonary vein

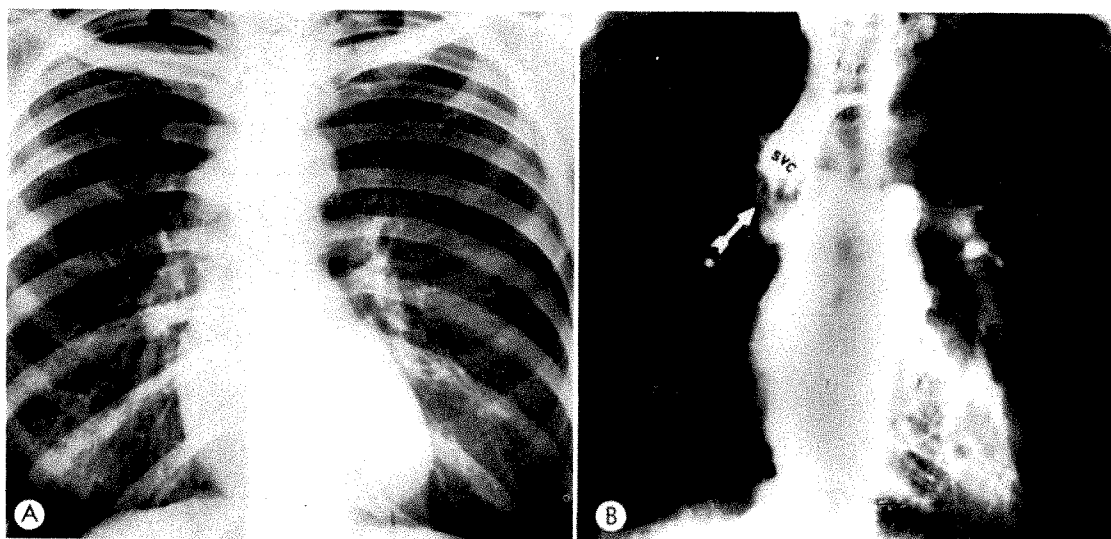


FIG. 1. Case 2. Partial drainage of the pulmonary veins into the superior vena cava. (A) Frontal teleroentgenogram showing prominence of the right upper hilus region. (B) Frontal angiogram with filling defect (arrow) due to anomalous insertion of the pulmonary veins into the superior vena cava (SVC).

insertion was not obtained by cardiac catheterization.

Function of Superior Vena Cava and Right Atrium. Three patients, all women with atrial septal defects (Cases 3, 4, and 5, Table 1), had partial drainage of the right pulmonary veins into the junction of the superior vena cava and the right atrium. The first patient (Fig. 2A) had striking right heart and pulmonary artery enlargement with plethoric lungs. Clinical and hemodynamic studies established the diagnosis of mitral stenosis. The angiocardiograms (Fig. 2, B,C and D) demonstrated a small but constant filling defect at the junction of the superior vena cava and the right atrium. The jet was located in the lateral and posterior part of the superior vena cava and was visible for several seconds after the beginning of the injection. The lateral as well as the frontal view showed the defect (Fig. 2C), and in addition there was reflux filling of the anomalous vein (Fig. 2D). Operation and autopsy established the presence of an anomalous right superior pulmonary vein entering the superior vena cava-right atrium junction.

The second patient with partial insertion of the pulmonary veins into the junction of

the superior vena cava and right atrium had moderate enlargement of the heart and pulmonary artery with plethoric lungs, especially of the right lower lung field (Fig. 3A). Angiocardiography also revealed a large triangular defect at the junction of the superior vena cava and right atrium (Fig. 3B). Later, at the time of left heart opacification, the pulmonary veins were seen to drain into the defect (Fig. 3C). At operation, the pulmonary veins of the right upper and middle lobes were indeed found to be connected with the superior vena cava. An ivalon sponge prosthesis was used to close the atrial septal defect and to shunt the anomalous veins into the left atrium.

Angiocardiographic study of the third patient (Case 5), who also had a rudimentary left superior vena cava draining into the right atrium via the coronary sinus, revealed a constant triangular filling defect at the junction of the superior vena cava and right atrium (Fig. 4, A and B).

Right Atrium. The 2 patients with transposed right pulmonary veins into the right atrium also had atrial septal defects. One patient was previously reported;¹² the other had a characteristic, large and constant defect in the outer, lower part of the right

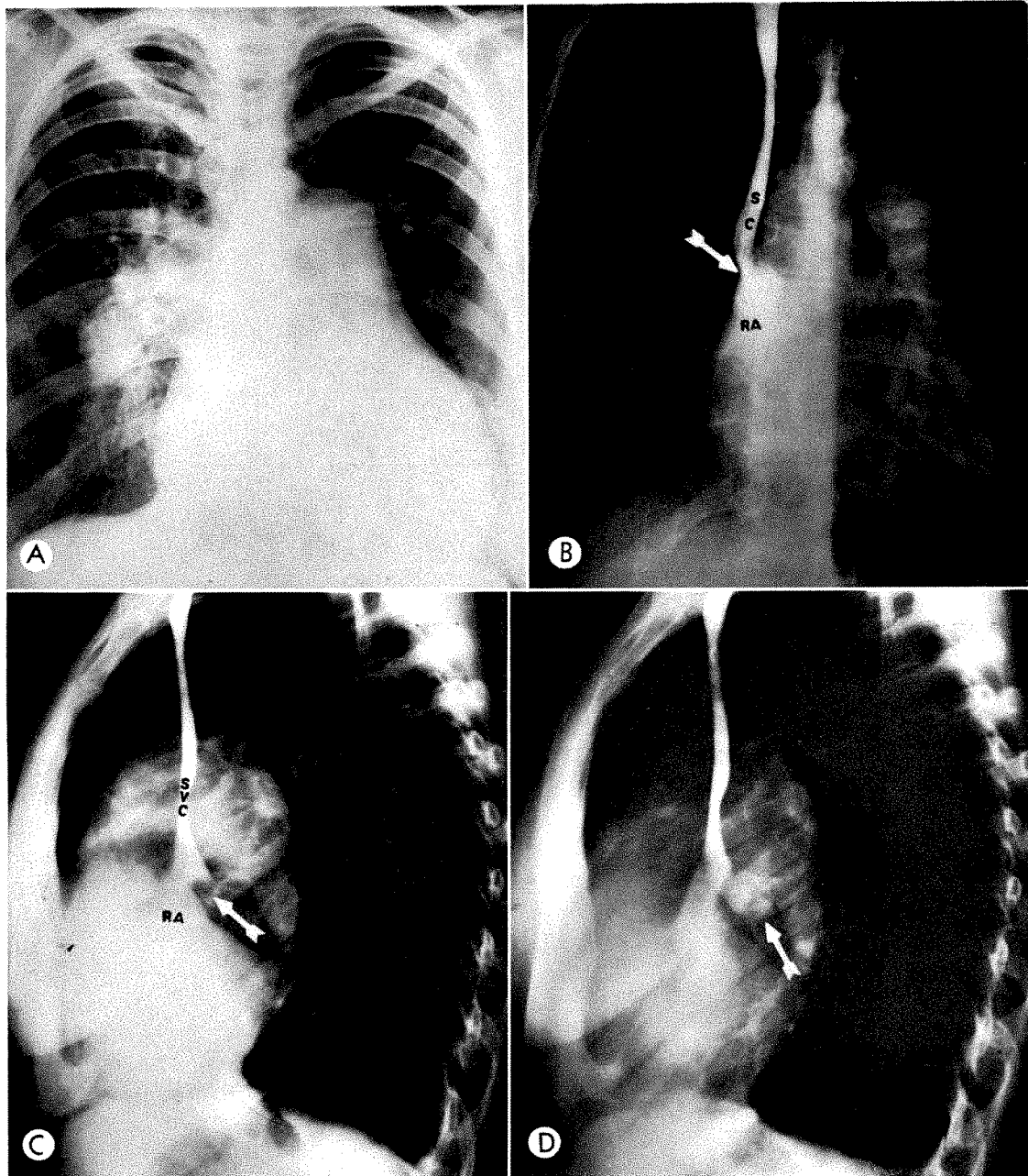


FIG. 2. Case 3. Partial insertion of the pulmonary veins at the junction of the superior vena cava and the right atrium. (A) Frontal teleroentgenogram showing marked enlargement of the heart, pulmonary artery and right branch. (B) Frontal angiogram showing filling defect (arrow) at junction of superior vena cava (SVC) and right atrium (RA). (C) Lateral angiogram with jet of unopacified material (arrow) at the junction of the superior vena cava (SVC) and the right atrium (RA). (D) Lateral angiogram showing reflux of contrast material (arrow) into the anomalous pulmonary vein.

atrium (Fig. 5, A and B). The presence of anomalous right pulmonary veins inserting into the right atrium was confirmed at operation.

Left Innominate Vein. Partial anomalous pulmonary venous drainage of the left lung into the left innominate vein was studied in 4 patients. In 1 (Case 11, Table 1) previ-

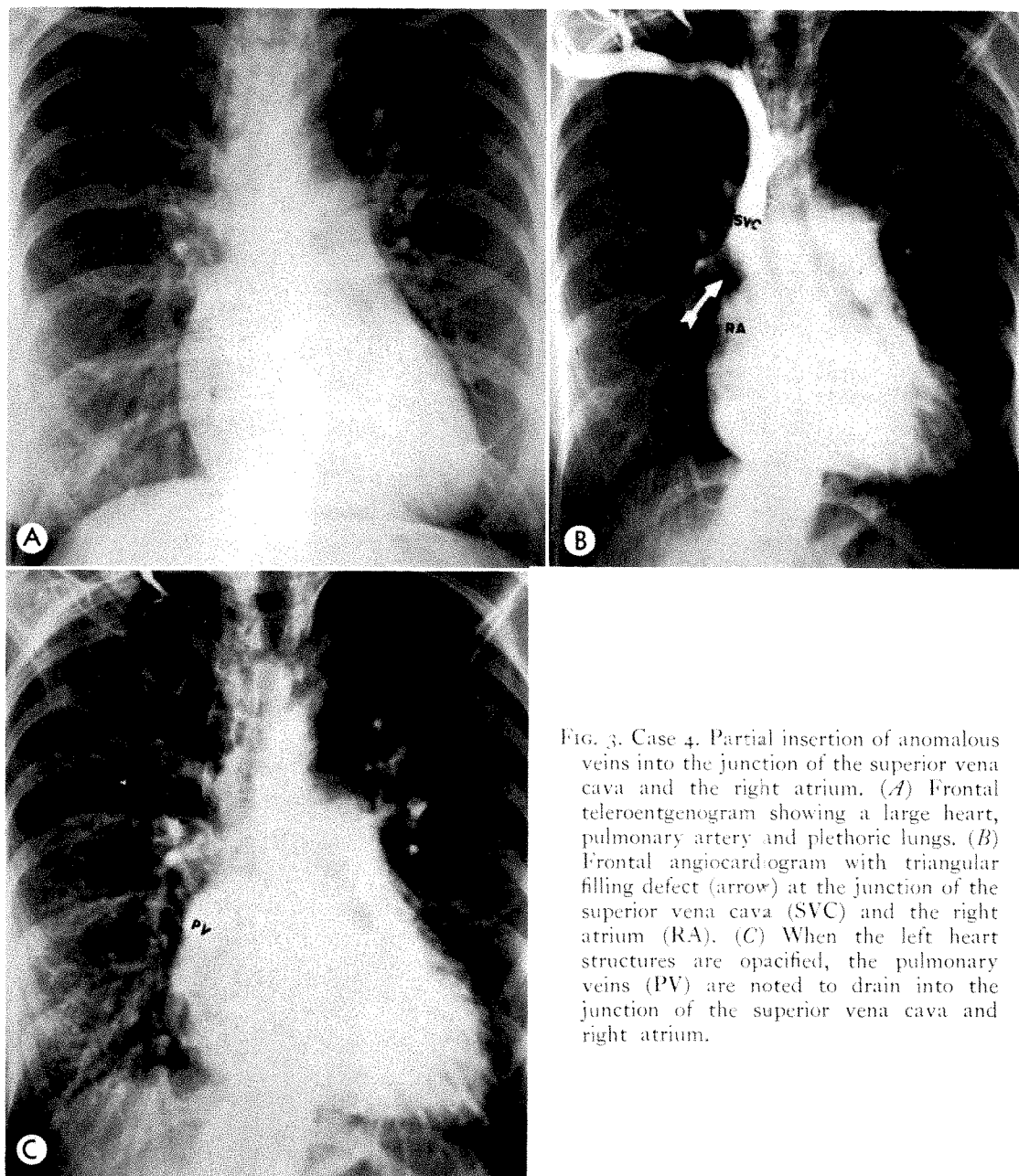


FIG. 3. Case 4. Partial insertion of anomalous veins into the junction of the superior vena cava and the right atrium. (A) Frontal teleroentgenogram showing a large heart, pulmonary artery and plethoric lungs. (B) Frontal angiocardogram with triangular filling defect (arrow) at the junction of the superior vena cava (SVC) and the right atrium (RA). (C) When the left heart structures are opacified, the pulmonary veins (PV) are noted to drain into the junction of the superior vena cava and right atrium.

ously reported,¹² the entire left lung drained via a common channel into a persistent left superior vena cava and thence into the left innominate vein. This patient also had rheumatic mitral stenosis. Left thoracotomy established the course of the anomalous pulmonary venous vessels; mitral valvuloplasty resulted in marked improvement of the patient. The conventional roentgeno-

gram of this patient, despite the fact that only the left pulmonary veins were transposed, showed the characteristic figure 8 deformity. Angiocardiography done via the left arm demonstrated a filling defect (jet) in the left innominate vein. Later, at the time of opacification of the left heart structures, an opacified, huge and persistent left superior vena cava was shown to be con-

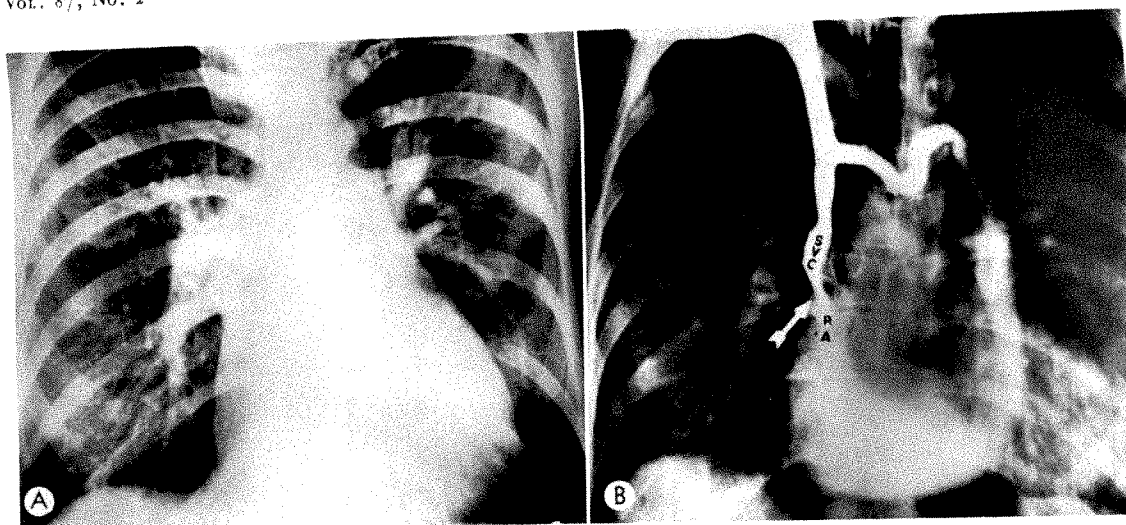


FIG. 4. Case 5. Partial insertion of the pulmonary veins into the junction of the superior vena cava and the right atrium. (A) Frontal teleroentgenogram showing a large heart, pulmonary artery and pulmonary vasculature. (B) Frontal angiogram discloses a nonopacified jet (arrow) at the junction of the superior vena cava (SVC) and the right atrium (RA). Note the left superior vena cava filled by reflux from an intercommunicating vein between the caeae.

nected with the left innominate vein at the site of the previous jet whereas the right pulmonary veins inserted into an enlarged left atrium.¹²

The 3 other patients in this group (Cases 8, 9 and 10) had only the left superior pulmonary vein draining into the left innominate vein. Case 8 was studied because of

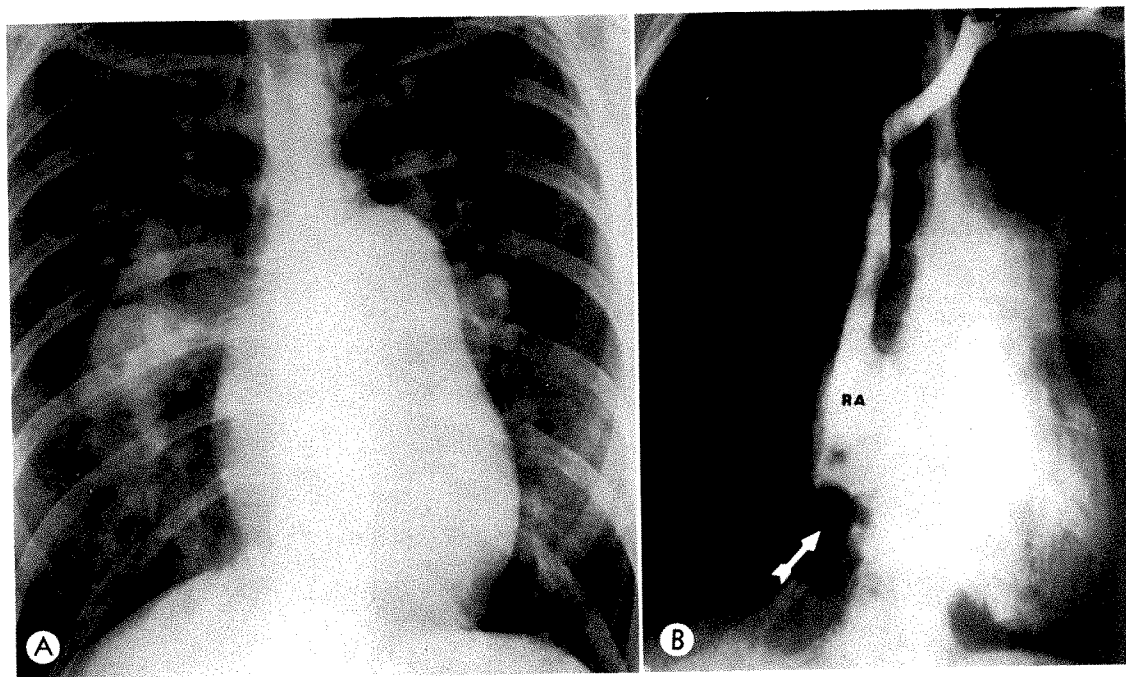


FIG. 5. Case 7. Partial drainage of the pulmonary veins into the right atrium. (A) Frontal teleroentgenogram revealing moderate cardiac enlargement, a huge pulmonary artery and branches, especially of the right lung. (B) Frontal angiogram with a huge filling defect (arrow) at the base of the right atrium (RA).

the finding of a mass in the upper left hilus on routine roentgen survey of the chest (Fig. 6A). Angiocardiography revealed a filling defect (jet) in the left innominate vein (Fig. 6B). Later, at the time of left heart opacification, the left superior pulmonary vein emptying into the left innominate vein was demonstrated (Fig. 6C). The younger patient (Case 9) had only a slight prominence of the left upper hilus on the conventional roentgenogram but merited further investigation because a murmur was heard over the left upper sternum. He, too, had the characteristic jet findings on the

angiocardigram. Case 10, a forty-eight year old man with heart failure, had insertion of the left pulmonary veins into the left innominate vein (Fig. 7, A, B and C). The cardiac catheterization data, especially dye dilution studies, excluded other congenital anomalies and indicated that the heart failure was due to left ventricular myocardial disease of unknown etiology.

TOTAL ANOMALOUS INSERTIONS OF PULMONARY VEINS

Function of Superior Vena Cava and Right Atrium. Only 1 patient (Case 12) with

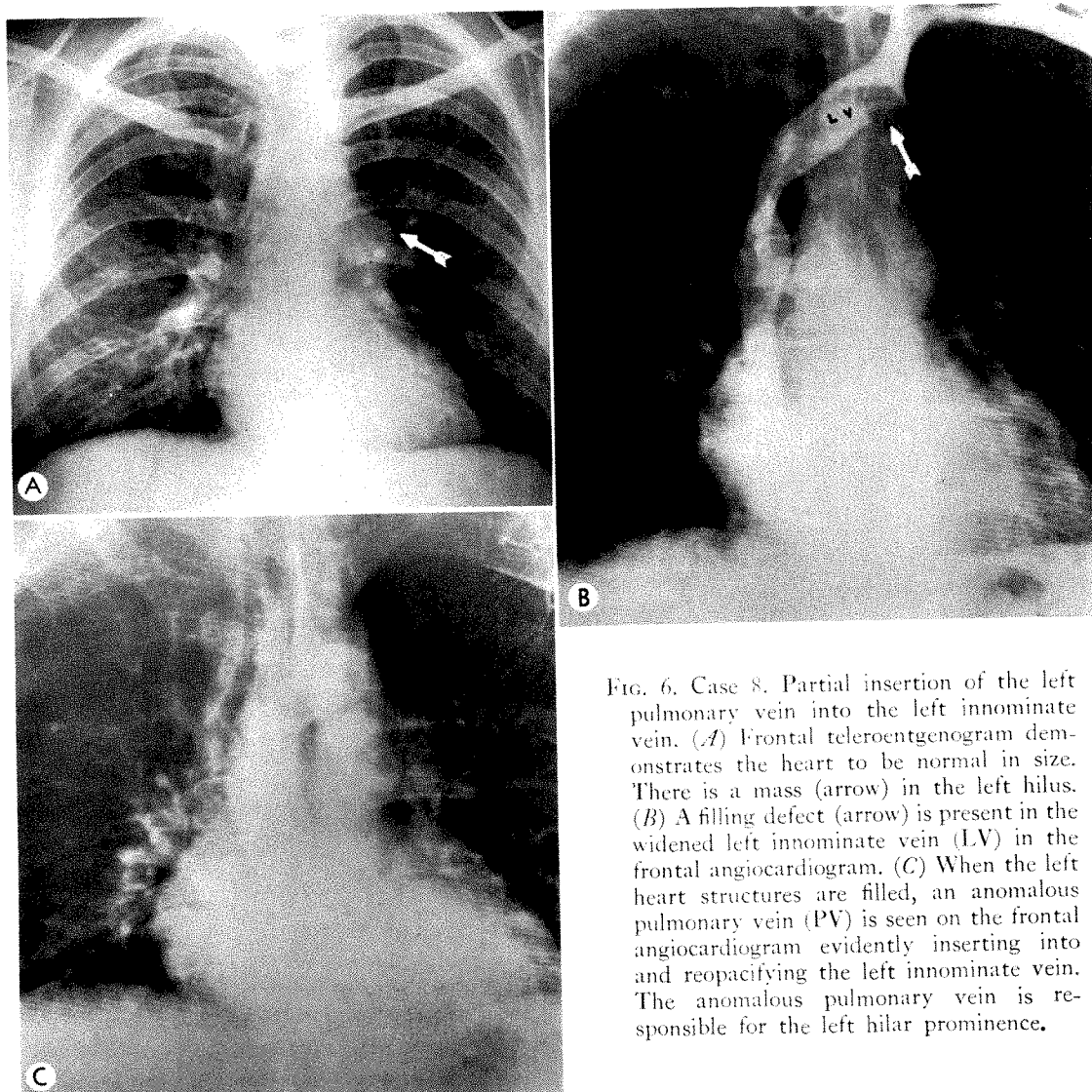


FIG. 6. Case 8. Partial insertion of the left pulmonary vein into the left innominate vein. (A) Frontal teleroentgenogram demonstrates the heart to be normal in size. There is a mass (arrow) in the left hilus. (B) A filling defect (arrow) is present in the widened left innominate vein (LV) in the frontal angiogram. (C) When the left heart structures are filled, an anomalous pulmonary vein (PV) is seen on the frontal angiogram evidently inserting into and reopacifying the left innominate vein. The anomalous pulmonary vein is responsible for the left hilar prominence.

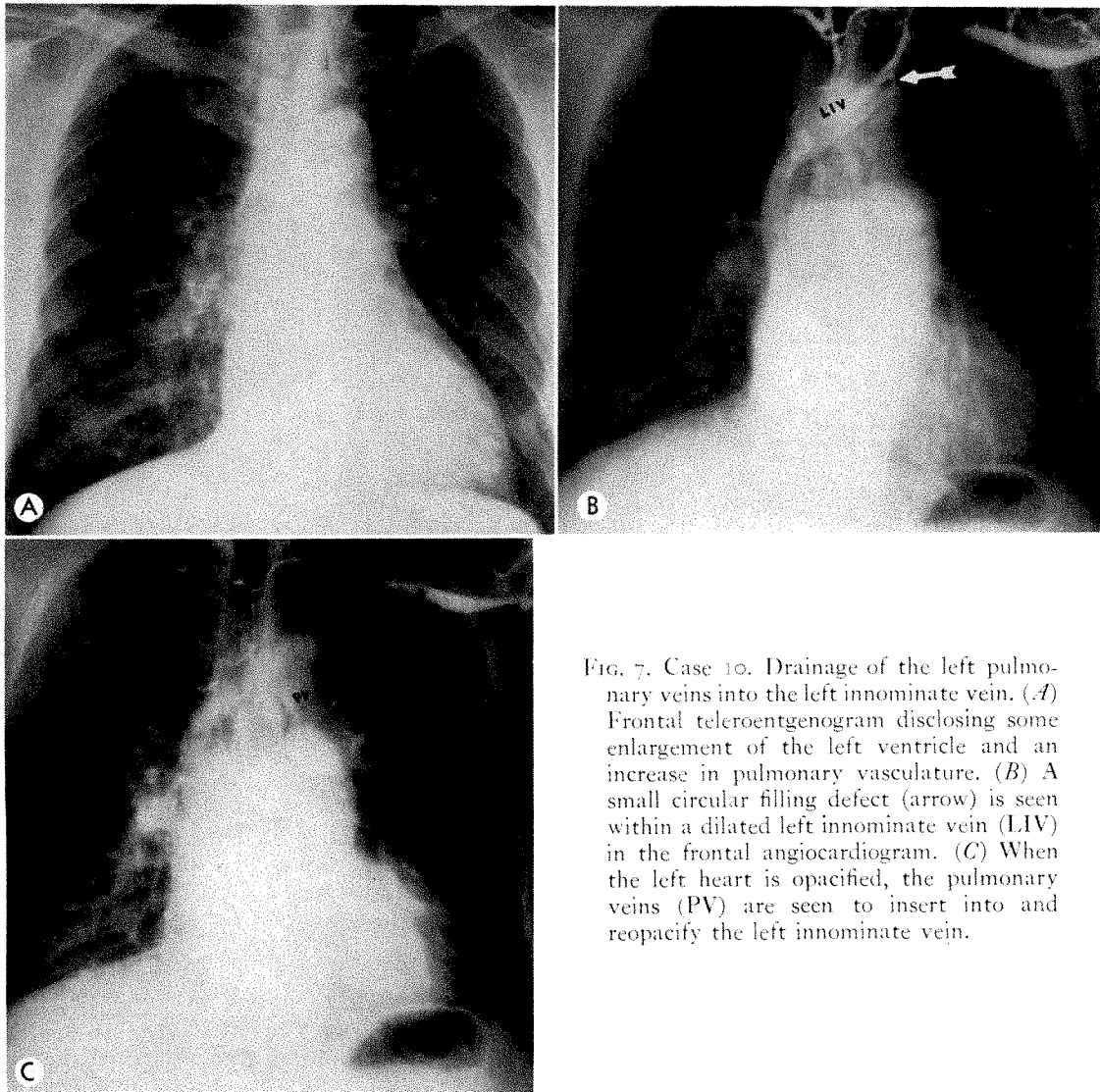


FIG. 7. Case 10. Drainage of the left pulmonary veins into the left innominate vein. (A) Frontal teleroentgenogram disclosing some enlargement of the left ventricle and an increase in pulmonary vasculature. (B) A small circular filling defect (arrow) is seen within a dilated left innominate vein (LIV) in the frontal angiogram. (C) When the left heart is opacified, the pulmonary veins (PV) are seen to insert into and reopacify the left innominate vein.

complete pulmonary venous insertions into the junction of the superior vena cava and the right atrium was studied; this case has been reported previously in detail.¹² A large triangular constant filling defect was clearly visualized and later, in the serial angiographic study and at the time of pulmonary venous opacification, a large pulmonary vein was demonstrated to be inserted into the area of the jet.

Right Atrium. Two patients with total pulmonary venous drainage into the right atrium (Cases 13 and 14) were encountered in this group. Case 13 was previously re-

ported.¹² The other patient had moderate enlargement of the heart and plethoric lungs, especially at the right base (Fig. 8A). A large filling defect involving the entire right atrium, in part probably also due to right-to-left shunting of blood through the atrial defect, was demonstrated (Fig. 8, B and C).

Left Innominate Vein. Two patients in the series had complete drainage of the pulmonary veins into the left innominate vein. The first case (previously reported¹²) recently died at the age of forty-six years and at autopsy the course of the total

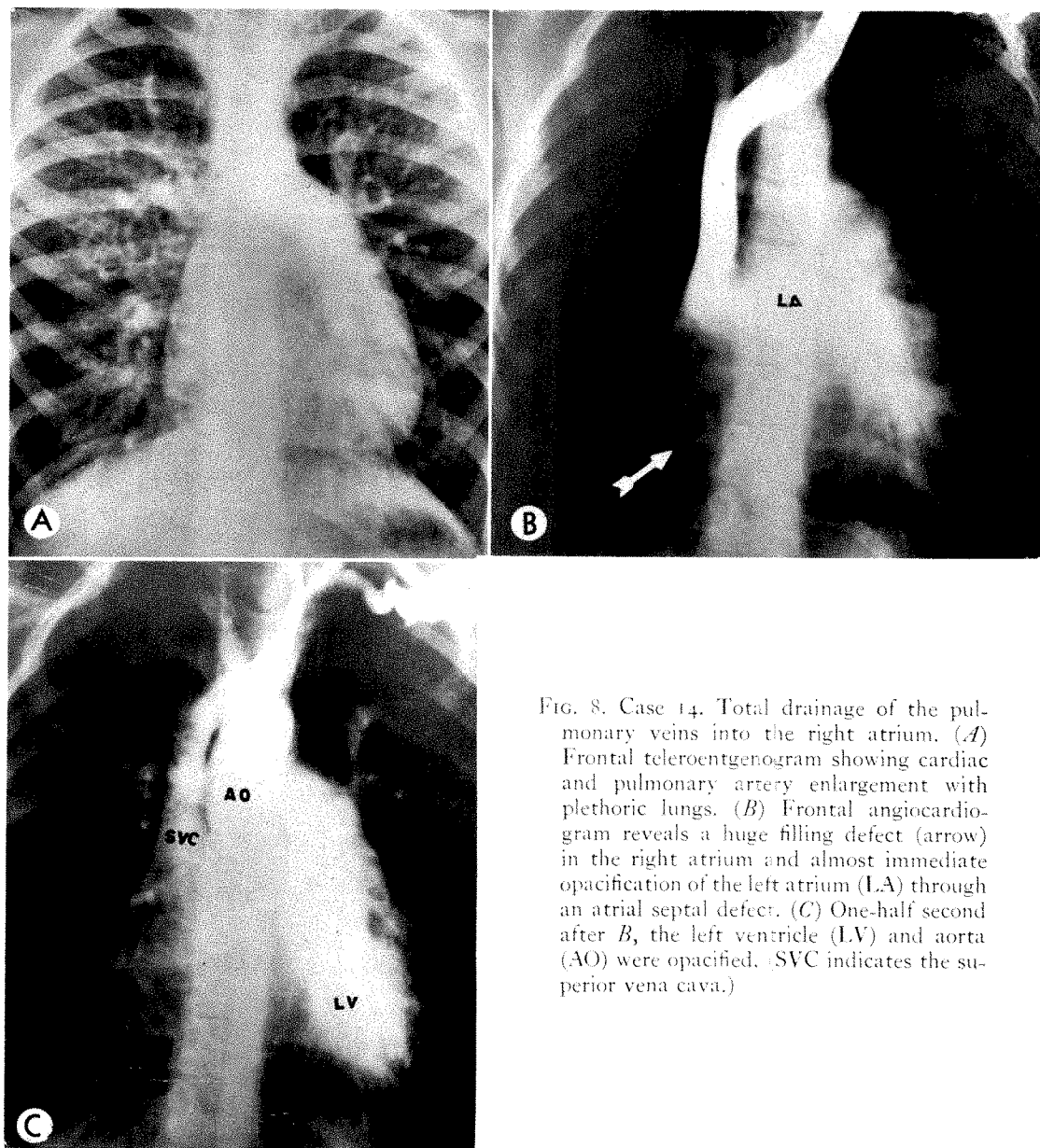


FIG. 8. Case 14. Total drainage of the pulmonary veins into the right atrium. (A) Frontal teleroentgenogram showing cardiac and pulmonary artery enlargement with plethoric lungs. (B) Frontal angiocardio-gram reveals a huge filling defect (arrow) in the right atrium and almost immediate opacification of the left atrium (LA) through an atrial septal defect. (C) One-half second after B, the left ventricle (LV) and aorta (AO) were opacified. SVC indicates the superior vena cava.)

anomalous pulmonary venous drainage into the left innominate vein was confirmed. The conventional roentgenograms showed the classic figure 8 configuration. The angiocardio-grams revealed a large filling defect of the left innominate vein and marked dilatation of the right superior vena cava. When the left cardiovascular structures were opacified, a large common venous channel from the right and left lungs was seen emptying into a hugely dilated persist-

ent left superior vena cava which, in turn connected with the left innominate vein.¹² The other patient, aged two months, also exhibited all the classic roentgen features of this anomaly (Fig. 9, A-D).

Coronary Sinus. An eight month old cyanotic infant with heart failure and total anomalous pulmonary venous drainage into the coronary sinus was studied angiocardio-graphically. There was tremendous enlargement of the heart, especially of the

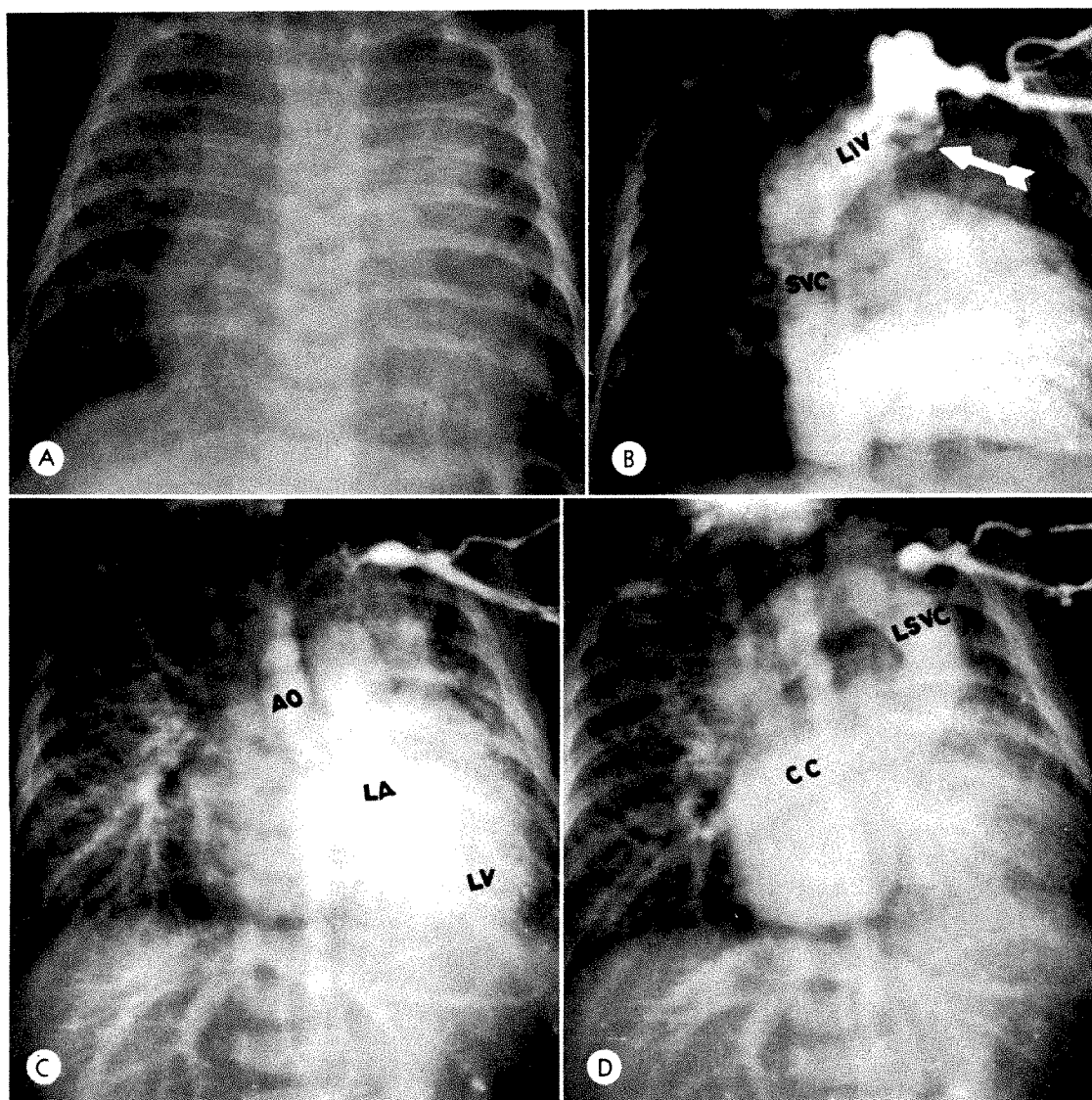


FIG. 9. Case 16. Total drainage of the pulmonary veins into the left innominate vein. (A) Frontal roentgenogram of a two month old infant exhibiting enlargement of the heart and supracardiac structures. (B) In the frontal angiogram the left innominate vein (LIV) contains a jet (arrow) and the superior vena cava (SVC) is dilated. (C) The angiogram taken immediately after B shows opacification of a small left atrium (LA), left ventricle (LV) and aorta (AO). (D) A later frontal angiogram shows a common channel (CC) collecting blood from the right and left pulmonary veins and proceeding via a left superior vena cava (LSVC) to reopacify the left innominate vein and the right superior vena cava.

right cardiac chambers (Fig. 10, A and B). Angiograms (Fig. 10, C, D and E) showed a large, rounded and constant filling defect in the right atrium. At necropsy (Fig. 10F), a dilated coronary sinus due to drainage of all the pulmonary veins was found. Two additional patients (Cases 18 and 19) also had a filling defect in the

region of the coronary sinus. In both instances cardiac catheterization and autopsy examination confirmed the diagnosis.

DISCUSSION

Filling defects in opacified cardiovascular structures were recognized soon after angiography became a practical pro-

cedure. Such defects may occur normally, when the contrast material first enters the great veins from the arm, and are due to mixing of unopacified blood from the opposite innominate vein, azygos vein or inferior vena cava. Filling defects may also be due to intraluminal invasion of the superior vena cava by lung cancer^{1,13,17} or to intracavitary tumors or thrombi.^{6,14} Aneurysms of the aortic sinuses cause filling defects in the right heart chambers and these are identified when they become opacified during left heart visualization.^{15,16}

The majority of the filling defects visualized during angiocardiology are due to the abnormal mixing of unopacified blood from either a cardiac chamber or vessel.⁴ Usually, the head of pressure is greater in the nonopacified structure and, as a result, a jet like effect is produced in the opacified structure when there is blood flow through the defect.

Disturbance of the uniform pattern of the contrasted cardiovascular structure has diagnostic significance. In 1951, Goetz⁵ called attention to a transient area of translucency in the left pulmonary artery due to the flow of unopacified blood from the aorta via a ductus. Soon after, Dotter and Stein-

berg² and Margulis and associates⁹ pointed out that the main stem pulmonary artery may also have unopacified blood as a result of blood flow through a ductus. In 1953, the significance of turbulence of contrast material in the right atrium due to tricuspid regurgitation was described.³ In 1955, the jet sign at the site of insertion of anomalous pulmonary veins was first described.¹² About that time, Swedish investigators^{7,8} also described the appearance of filling defects with intracardiac shunts. It follows that, if contrast material is injected directly into vessels or chambers with abnormal shunts, the opaque medium will flow through the shunt. A jet of contrast material will result, whereas before a negative or filling defect was seen. This is well illustrated in Figures 3C, 6C, 7C and 9D wherein pulmonary veins were opacified at the time of left heart filling and can be seen to fit into the respective defect areas.

The jet sign associated with pulmonary venous drainage into the superior vena cava (Fig. 1B) may be difficult to distinguish from the filling defects normally produced by inflow of nonopacified blood from the opposite innominate or the azygos vein. Usually these defects are less well defined,

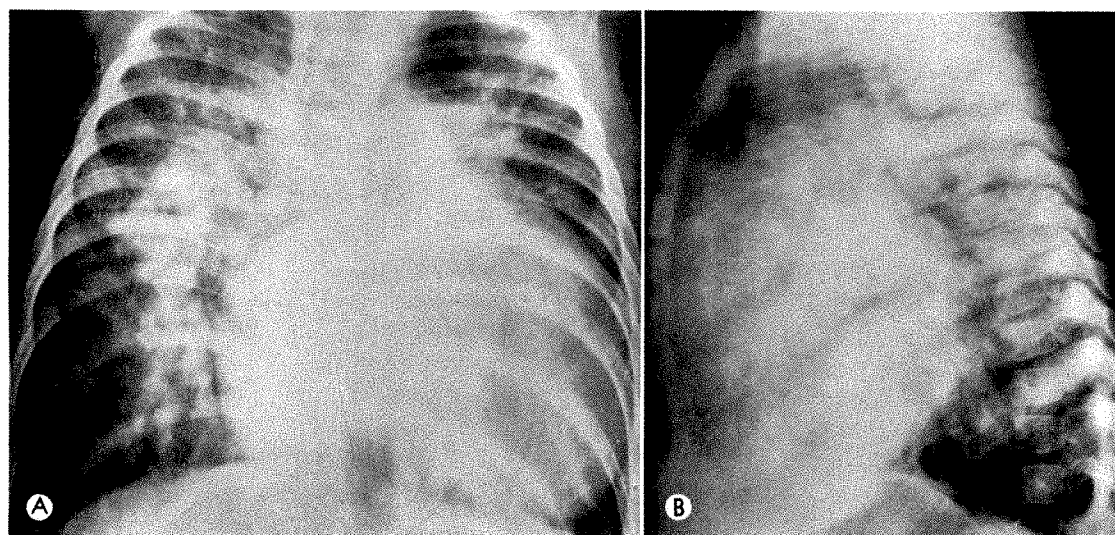


FIG. 10. Case 17. Total anomalous pulmonary venous drainage into the coronary sinus. (A) Frontal teleroentgenogram exhibiting a very large heart and pulmonary artery with striking pulmonary congestion. (B) Lateral teleroentgenogram showing that the right heart is huge.

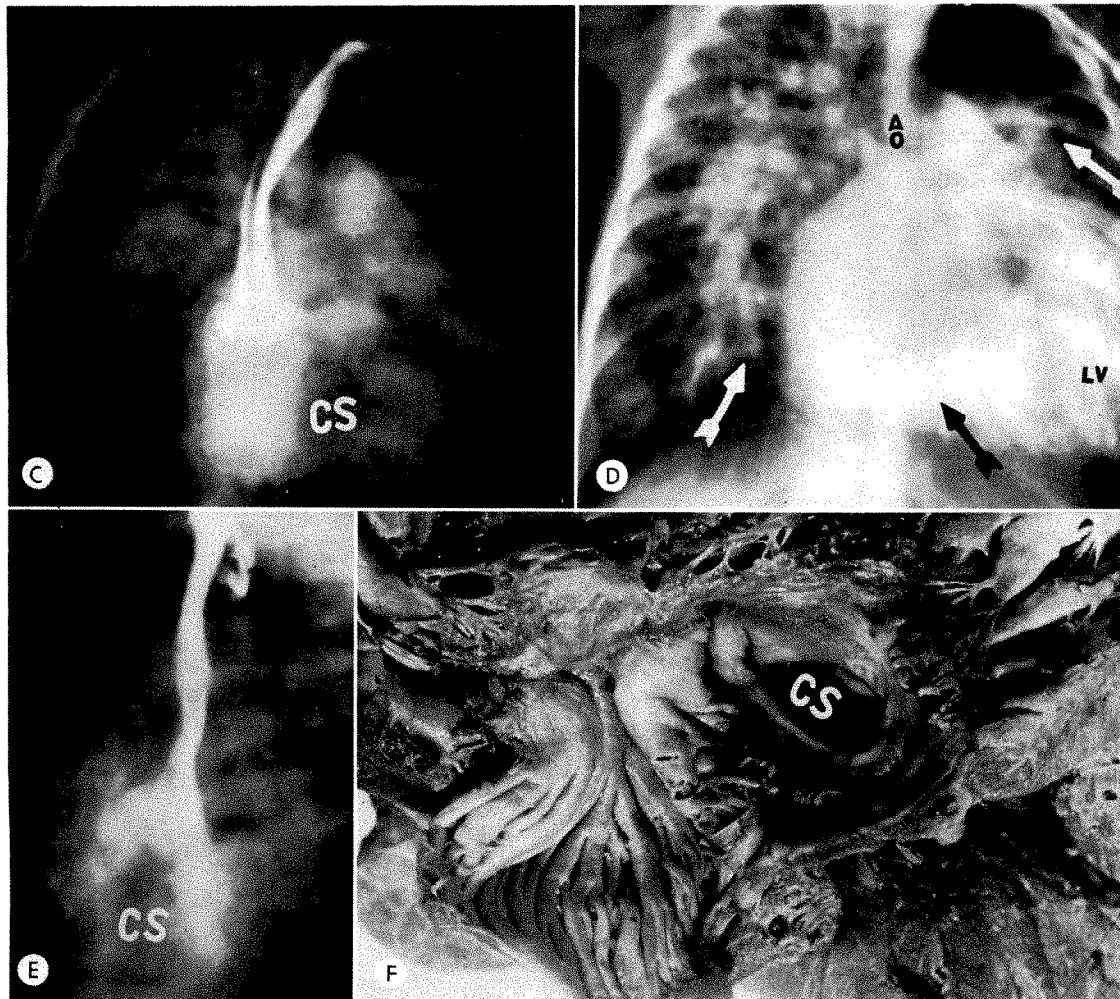


FIG. 10. (C) Frontal angiogram revealing enlargement of the right atrium with a large rounded filling defect in the region of the coronary sinus (CS). (D) When the left heart structures (pulmonary veins [white arrows], left ventricle [LV], and hypoplastic aorta [AO]) become opacified, the coronary sinus (black arrow) is also opacified. This demonstrates that the pulmonary veins drain into the coronary sinuses. (E) Lateral angiogram showing a filling defect in the coronary sinus (CS) at the time of right atrial opacification. (F) The postmortem specimen shows the greatly dilated coronary sinus (CS).

transient, smaller, and not as consistent in shape as those due to anomalous pulmonary veins (Fig. 1A). Later, when the anomalous pulmonary vein becomes opacified, it may be traced to the site of entrance into the superior vena cava and help to confirm the diagnosis. Similarly, reflux filling of an anomalous pulmonary vein with contrast substance aids in establishing the diagnosis (Fig. 2C).

Pulmonary veins that insert at the junction of the superior vena cava and right atrium have a characteristic triangular fill-

ing defect (Fig. 2B, 3B, and 4B). When the pulmonary veins become opacified, it may be possible to identify the course of the anomalous vein. The adjacent opacified left atrium, however, may make it difficult to distinguish the course of the anomalous vein.

It may be difficult if not impossible to differentiate between filling defects in the right atrium due to large atrial defects and those caused by anomalous pulmonary veins. Indeed, in a recent case, angiocardiology supported by cardiac catheteriza-

tion findings warranted the diagnosis of anomalous insertions of all the pulmonary veins into the right atrium. Yet at operation and later at autopsy, a huge atrial septal defect alone was responsible for the filling defect. Figure 8B shows a huge defect in the right atrium believed to be due to anomalous pulmonary venous drainage. It seems unlikely that the left-to-right atrial shunt alone is of sufficient magnitude to cause the right atrial filling defect.

When anomalous pulmonary veins insert into the left innominate veins, there is a clearly defined filling defect at the site of entrance of the pulmonary vein (Fig. 6B, 7B and 9B).¹² Since this site is at some distance from the left atrium, the opacified anomalous vein can be clearly identified (Fig. 6C, 7C and 9D). When anomalous pulmonary veins inserting into the left innominate vein are suspected, and in order to demonstrate a filling defect, it is important to make the injection via the left arm. In a recent case, angiocardiology performed through injection of the right arm failed to show pulmonary veins that entered a persistent left superior vena cava.

The demonstration of a filling defect in the right atrium due to complete insertion of the pulmonary veins into the coronary sinus (Fig. 10, C, D and E) is of considerable importance, since it is difficult to differentiate drainage at this site from drainage into the right atrium.¹¹

Cardiac catheterization and dye dilution studies are important aids in the diagnosis of anomalous pulmonary veins. Both methods, however, may be found wanting. Often, when there is a high atrial septal defect, the catheter may seem to go directly into a pulmonary vein. Only when fluoroscopic or roentgen studies in oblique or lateral positions are made is it realized that the catheter has traversed the septal defect and entered the left atrium and a pulmonary vein. A dye dilution curve recorded after injection of dye into the pulmonary vein usually demonstrates whether or not it drains anomalously, although if a right-to-left shunt is also present differentiation from a normally draining vein may be

difficult. In such circumstances, the jet sign will establish the diagnosis on an anatomic rather than on a functional basis.

SUMMARY AND CONCLUSIONS

In 19 patients with anomalous pulmonary venous drainage a characteristic jet at the site of insertion of the anomalous vein was recognized on the angiocardiology. The filling defect is due to unopacified blood from the pulmonary vein entering an opacified vessel or cardiac chamber. Filling defects in the superior vena cava may occur normally due to blood flow from the opposite innominate or the azygos vein. The location of the defects will quickly identify normal channels. Defects in the superior vena cava due to neoplastic invasion may be readily recognized by the presence of extensive venous collateral circulation.

In the right atrium, filling defects due to atrial tumors, tricuspid regurgitation, atrial septal defects and inferior vena caval blood flow may make recognition of transposed pulmonary veins difficult. Clinical, angiocardiology and hemodynamic studies should allow the differentiation of all the above lesions.

The jet sign is a more reliable indication for the diagnosis of anomalous pulmonary venous drainage than is the passing of a catheter into the pulmonary vein. Unless oblique and lateral roentgenograms of the chest are made with the catheter *in situ*, passage through a left atrium may be unrecognized. Accordingly, angiocardiology is a valuable adjunct in the preoperative diagnosis of anomalous pulmonary venous drainage.

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ADDENDUM

Since this paper was submitted for publication, twelve additional patients have had angiocardiology demonstration of jets due to anomalous pulmonary venous drainage.

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ANGIOGRAPHIC PATTERNS OF CEREBRAL CONVEXITY VEINS AND SUPERFICIAL DURAL SINUSES

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IN RECENT years considerable interest has been concentrated on the angiographic appearance of the deep cerebral veins. Only scanty attention, however, has been devoted to the superficial veins of the brain. It is generally agreed that these veins constitute an irregular network with a multitude of different patterns, each with a large number of variations. Gvozdanović,⁸ who has worked systematically on the angiography of the superficial veins of the brain, stated in 1956 that these veins are "the stepchild of neuroradiologic diagnosis." This statement is still valid today.

Two preliminary observations led to the present study: (1) the convexity veins did not appear to be situated at random and (2) the superficial venous discharge in the two hemispheres only seldom seemed comparable in one and the same patient. The study was expanded by including observations on the superficial dural sinuses with particular regard to hemispheric differences.

PRESENT STUDY

The following vascular channels have been the object of our angiographic observations: superficial frontal, parietal and occipital veins with the vein of Trolard, superficial sylvian vein, vein of Labbé, superior longitudinal sinus, sinus rectus and transverse sinuses.

The superficial veins of the brain are arranged like the spokes of a wheel radiating from the hub—the stem of the sylvian fissure (Fig. 1, *A* and *B*). The radiate arrangement of the superficial cerebral veins has been the object of considerable discussion among anatomists (Symington,¹⁷ 1882; Sargent,¹⁵ 1911; Stopford,¹⁶ 1930; O'Connell,¹³ 1934). Some authors have attributed a functional significance to this peculiar distribution of the superficial veins; O'Connell¹² offered convincing evidence that this arrangement, which is not present in the early fetal brain, is the result of the centrifugal growth of the cerebral hemispheres.

The superficial frontal, parietal and oc-

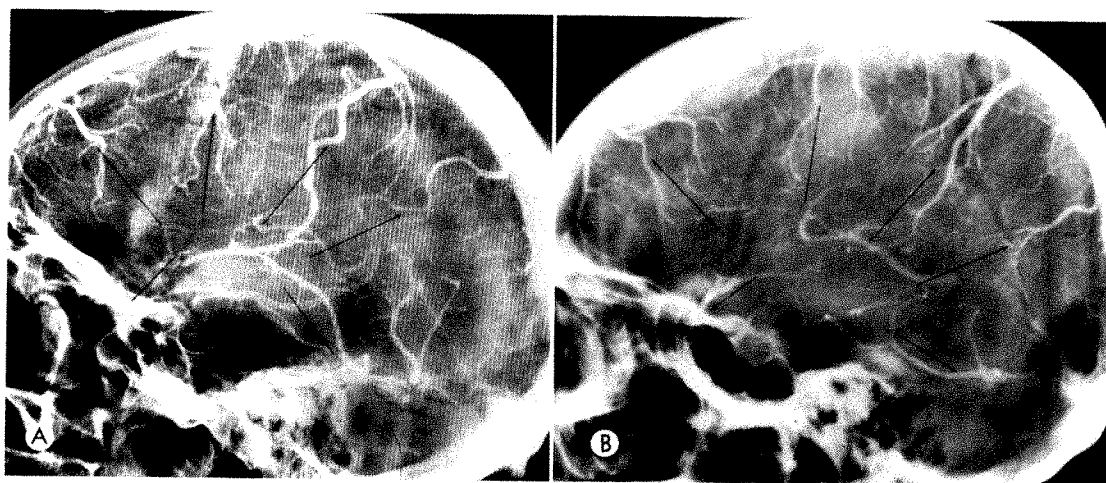


FIG. 1. (*A* and *B*) Superficial cerebral veins (note spoke-like arrangement).

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capital veins are eight or ten in number and have a reasonably comparable angiographic caliber except for the vein of Trolard. This vein, also known as great anastomotic, superior anastomotic, or post-central channel, is the largest superficial vein draining towards the superior longitudinal sinus from the sylvian region. Most frequently, it is located at the level of the central sulcus or a little more posteriorly (Fig. 2); occasionally it is directed anteriorly towards the frontal pole—the “prefrontal” vein of Trolard (Fig. 3). Sometimes two large superficial veins drain towards the superior longitudinal sinus with approximately the same caliber—the “double” vein of Trolard (Fig. 4). Because of its caliber, the vein of Trolard is clearly recognized on anteroposterior angiograms (Fig. 5).

The superficial sylvian (superficial middle cerebral) vein winds around the anterior pole of the temporal lobe and enters the cavernous sinus (Fig. 6–10).

The vein of Labbé (inferior anastomotic) connects the sylvian region with the transverse sinus (Fig. 11, *A* and *B*). Frequently, one sees a double vein of Labbé, the anterior almost always larger than the posterior. The latter originates from the fusion of two branches, one from the area of the supra-marginal and angular gyri, and one from the posterior external occipital surface (Fig. 12). The posterior vein of Labbé may fill via the vertebral artery. The anterior vein of

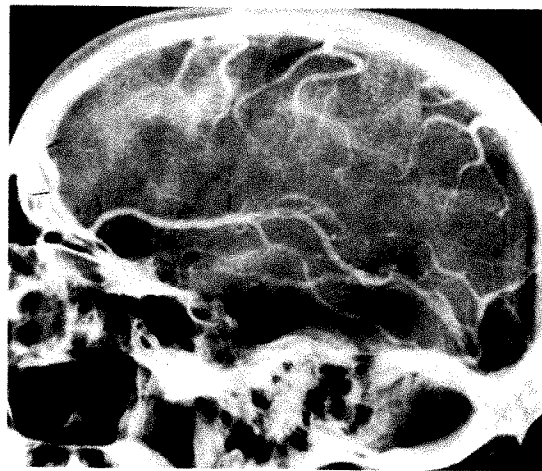


FIG. 3. Prefrontal vein of Trolard.

Labbé is easily discernible on anteroposterior angiograms (Fig. 13).

The three main superficial venous channels (Trolard, sylvian and Labbé) have occasionally a comparable size. In the great majority of cases, however, one or two of these channels “stand out” because of their larger caliber. This predominance has been the object of the first part of the present study. Only “normal” carotid angiographies with satisfactory venous phases have been included. Seriograms taken within three to five seconds after carotid injection were used which, according to Greitz,⁷ are best to evaluate the convexity veins. Table 1 shows the incidence of the superficial venous predominance found in a series of

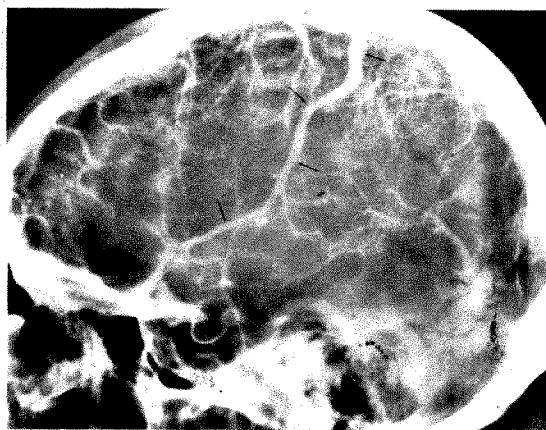


FIG. 2. Vein of Trolard.



FIG. 4. Double vein of Trolard.

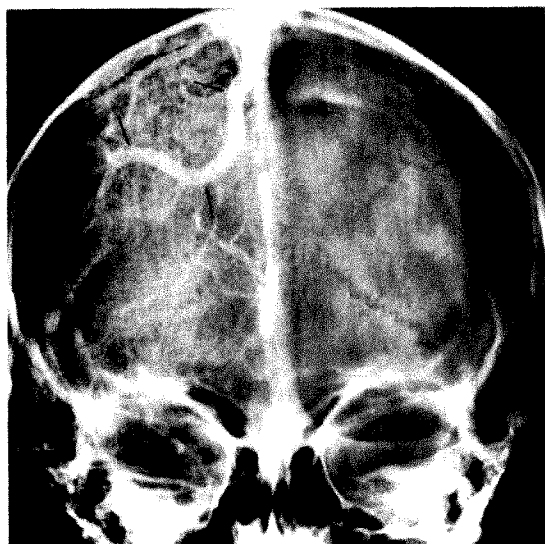


FIG. 5. Vein of Trolard on the anteroposterior angiogram.

180 normal carotid angiographies.

The superficial phlebograms in the left and right hemispheres of each of 65 patients were compared (Table II). These included only those cases in which the venous phases in the two hemispheres were comparable in timing and technical quality. The venous discharge in the two hemispheres was different in 56 cases and similar in 9. The predominant pathways of venous discharge in the two hemispheres of the 65 cases are shown in Table III. In a significant number

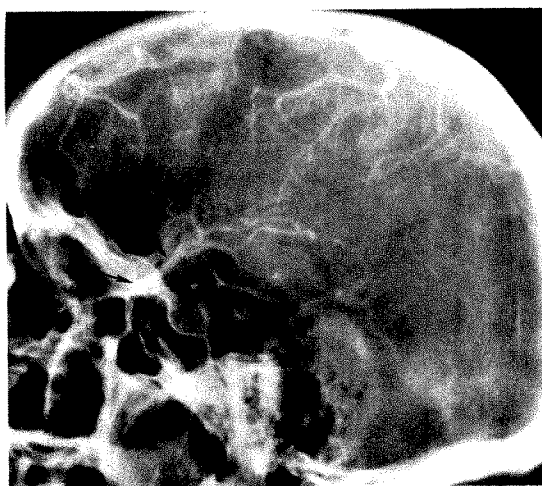


FIG. 6 Superficial sylvian vein.

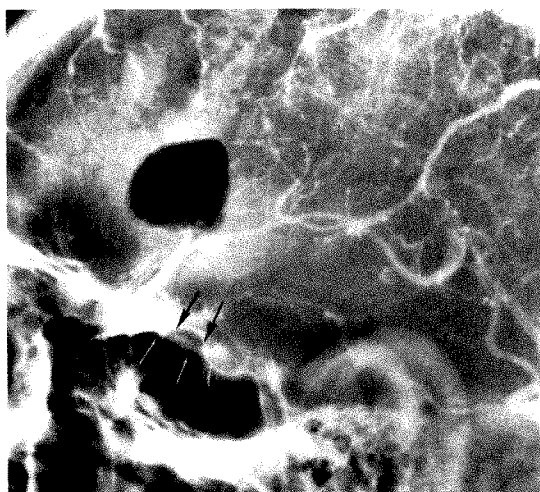


FIG. 7. Superficial sylvian vein (draining towards cavernous sinus).

of cases of the present series, the predominant superficial venous channel in the left hemisphere was the vein of Labbé (Fig. 14A), while the vein of Trolard predominated in the right (Fig. 14B). No significant morphologic differences have been previously found anatomically or roentgenographically in the two normal hemispheres. The functional hemispheric dominance has no demonstrated morphologic counterpart. Our findings on the hemispheric differences



FIG. 8. Contrast-filling of cavernous sinus from superficial sylvian vein.

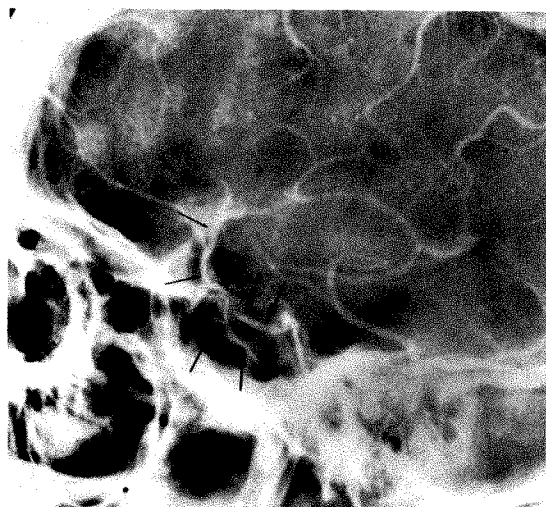


FIG. 9. Superficial sylvian vein (small arrows) emptying into cavernous sinus. Note "negative image" of contrast-emptied carotid syphon within contrast-filled cavernous sinus (large arrows).

in the superficial venous discharge of the brain were somewhat intriguing and we have endeavoured to relate these findings to the results of Wada's test which assesses hemispheric dominance. The Wada test, which is reasonably reliable, consists of injecting 125-150 mg. of sodium amytal into first one, then, about forty-five minutes later, the other carotid artery. Usually the patient will have dysphasic symptoms only after injection of the dominant side.

In 58 of our patients the Wada test was performed with unequivocal result. In 43, technically satisfactory carotid angiographies with good venous phases were also obtained (bilateral in 29 and unilateral in 14 cases). Of these the Wada test indicated a left cerebral dominance in 34 cases and a right dominance in 9. Table IV illustrates the handedness, the cerebral dominance as judged from Wada's test, and the hemispheric superficial venous predominance found in these patients. In the group of 9 patients with right hemispheric dominance, Labbé's vein was predominant on the right in 6 and on the left in 1 case, while it was equal to the larger remaining vessels (Trolard and/or sylvian) in 3 cases on the left and in no instance on the right. In this same

TABLE I
INCIDENCE OF PROMINENT SUPERFICIAL
PATHWAYS OF VENOUS DRAINAGE

Vein	No. of Cases	Per Cent
Trolard	58	32.2
Labbé	72	40.0
Sylvian	14	7.7
Trolard and Labbé	21	11.6
Trolard and Sylvian	3	1.6
Labbé and Sylvian	6	3.3
Trolard, Labbé and Sylvian of Similar Caliber	6	3.3
	180	

group Trolard's vein was predominant in 5 cases on the left and in 1 case on the right, while it was equal to the other vessels (Labbé and/or sylvian) in 1 case on the right and 3 on the left (Table V). In the group of 34 patients with left hemispheric dominance, Labbé's vein was predominant on the left in 18 cases and on the right in 2, while it was equal to the remaining vessels in 9 cases on the right and in 8 on the left.



FIG. 10. Superficial sylvian vein on the anteroposterior angiogram.

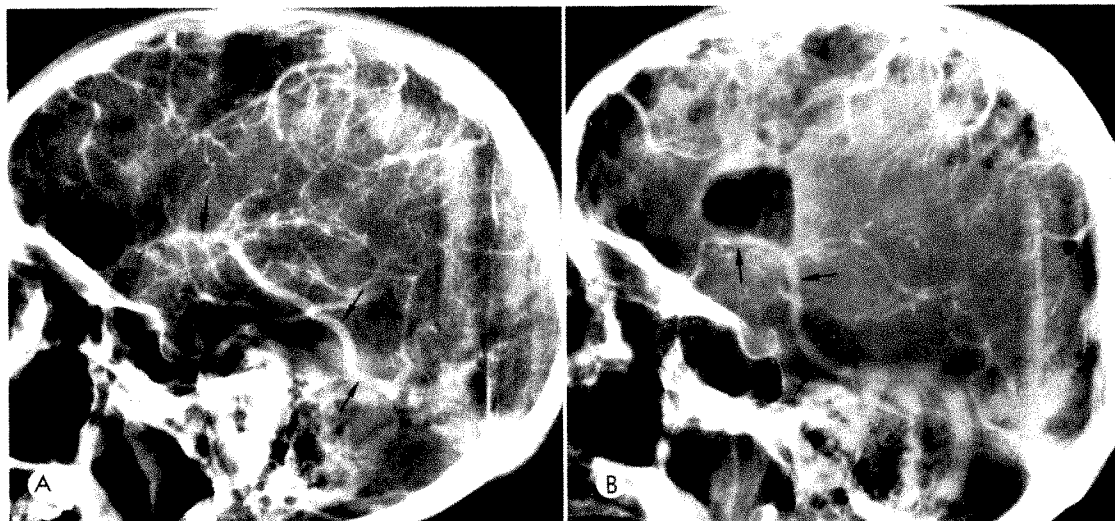


FIG. 11. (*A* and *B*) Two types of Labbé's veins.

Trolard's vein, on the other hand, was predominant on the right in 11 cases and on the left in 2, while it was equal to the other vessels in 10 cases on the right and in 8 on the left (Table vi).

The above data were analyzed statistically utilizing the chi-square test. The correlation showed that: (1) the vein of Labbé predominates in the dominant hemisphere with a significant probability, $P \leq .01$; (2) the vein of Trolard predominates in the nondominant hemisphere with a significant probability, $P \leq .01$; and (3)

the combination—Labbé's vein predominant in the dominant hemisphere, Trolard's vein predominant in the nondominant hemisphere—also has a significant probability, $P \leq .01$ (Fig. 15, *A* and *B*). It should be noted that in this statistical study the cases in which two or three channels were,

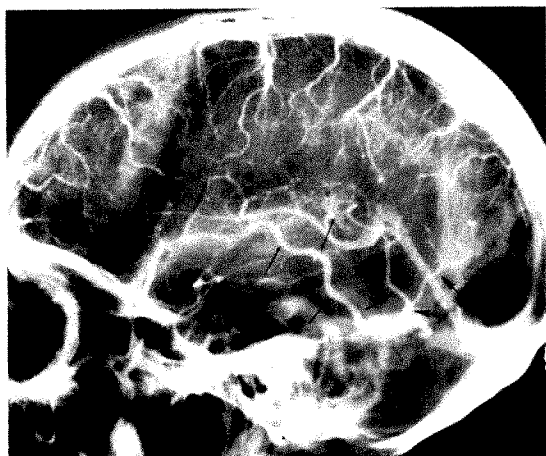


FIG. 12. Anterior vein of Labbé (small arrows). Posterior vein of Labbé forming from the fusion of two branches (large arrows).



FIG. 13. Vein of Labbé on the anteroposterior angiogram.

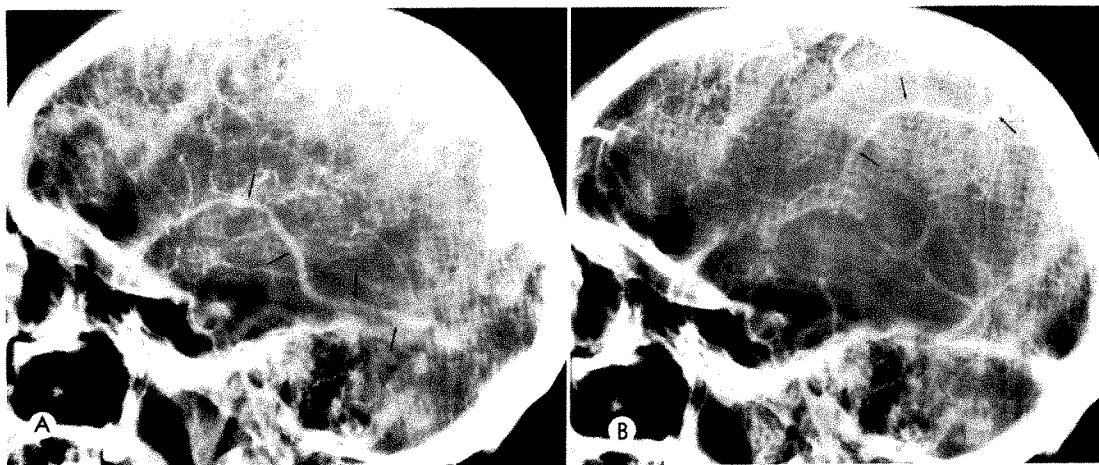


FIG. 14. (A) Vein of Labbé "predominant" in left hemisphere; (B) vein of Trolard "predominant" in right hemisphere (same patient).

in the same hemisphere, of approximately equal size were considered as frequency of one-half and one-third, respectively.

A study of the relative caliber of the superficial veins of brain specimens was attempted. However, after observing 20 specimens from non-neurologic patients, it became evident that such a study was not feasible; the collapse of the superficial cerebral veins was marked, and the different degrees of replenishment of the various channels were probably the result of the terminal phenomena or of postmortem positioning of the head.

The superficial convexity veins are tributaries of the superior longitudinal sinus, the cavernous sinuses, and the transverse sinuses. Occasionally, the superficial sylvian vein drains into the sphenoparietal sinus, and the vein of Labbé into the superior petrous sinus. An angiographic study of the superficial dural sinuses is feasible either by injecting directly into one of the sinuses (preferably the superior longitudinal as with the technique of Frenckner¹) or by the late seriograms of standard carotid angiographies. According to Greitz,⁷ a good demonstration of the superior longitudinal sinus

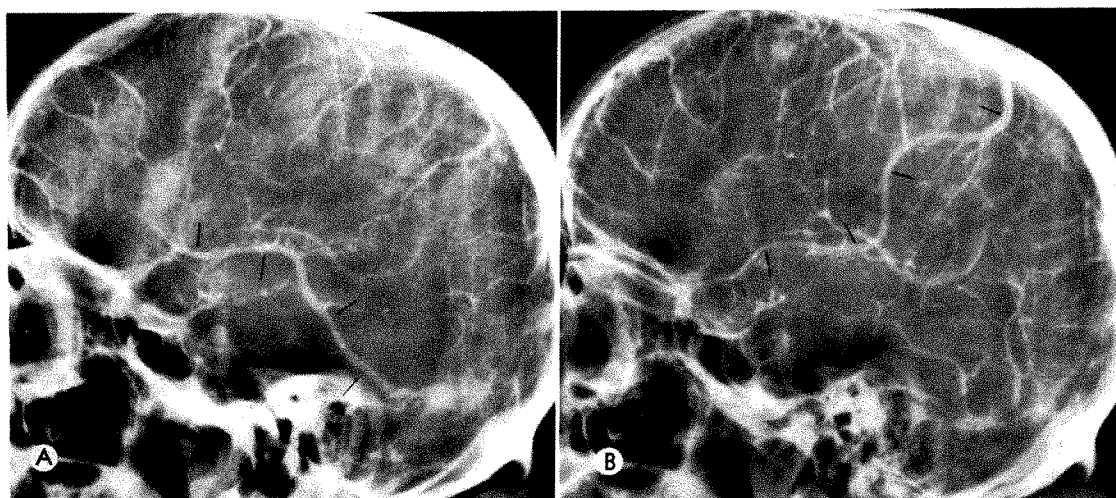


FIG. 15. (A) Vein of Labbé "predominant" on right and (B) vein of Trolard on left (patient left handed with Wada's test pointing to right hemispheric dominance).

TABLE II
INDIVIDUAL PREDOMINANT SUPERFICIAL PATHWAYS OF VENOUS DRAINAGE

Case No.	Left Hemisphere							Right Hemisphere						
	Trolard	Labbé	Sylvian	Trolard + Labbé	Trolard + Sylvian	Sylvian + Labbé	Trolard + Labbé + Sylvian	Trolard	Labbé	Sylvian	Trolard + Labbé	Trolard + Sylvian	Sylvian + Labbé	Trolard + Labbé + Sylvian
1		+						+						
2	+									+				
3	+								+					
4					+				+					
5		+							+					
6		+								+				
7						+		+						
8	+								+					
9	+								+					
10		+											+	
11		+						+						
12	+								+					
13							+	+						
14					+								+	
15							+			+				
16			+					+						
17							+	+						
18		+							+					
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21	+									+				
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32				+				+						
33		+						+						
34			+						+					
35		+						+						
36		+						+						
37		+						+						
38		+						+						
39		+						+						
40						+				+				
41		+												+
42	+										+			
43		+						+						

TABLE II (Continued)

Case No.	Left Hemisphere							Right Hemisphere						
	Trolard	Labbé	Sylvian	Trolard + Labbé	Trolard + Sylvian	Sylvian + Labbé	Trolard + Labbé + Sylvian	Trolard	Labbé	Sylvian	Trolard + Labbé	Trolard + Sylvian	Sylvian + Labbé	Trolard + Labbé + Sylvian
44		+										+		
45		+						+						
46	+								+					
47		+										+		
48		+						+						
49	+										+			
50		+							+					
51		+								+				
52		+							+					
53		+									+			
54		+						+						
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56							+	+						
57		+							+					
58				+							+			
59		+									+			
60			+					+						
61					+			+						
62	+								+					
63		+									+			
64					+			+						
65						+			+					

is usually obtained four to six seconds, and of the transverse sinuses six to eight seconds, after the commencement of the carotid injection. Our angiographic observations regarding the normal superficial dural sinuses have been carried out by seriographic carotid angiographies with the specific purpose of studying the symmetry of drainage at the level of the confluence of sinuses (torcular Herophili). Anatomic studies carried out by others have demonstrated that an asymmetric arrangement of the superior longitudinal sinus, the sinus rectus and the transverse sinuses is frequent at the level of the torcular Herophili. Generally, the sinus rectus empties into the left, and the superior longitudinal sinus into the larger right transverse sinus. The arrangement of these large venous channels

TABLE III

HEMISPHERIC INCIDENCE OF PREDOMINANT SUPERFICIAL PATHWAYS OF VENOUS DRAINAGE

Vein	Left Hemisphere		Right Hemisphere	
	No. of Cases	Per Cent	No. of Cases	Per Cent
Trolard	12	18.4	30	46
Labbé	36	55	16	24.6
Sylvian	3		5	
Trolard+Labbé	2		7	
Trolard+Sylvian	4		3	
Labbé+Sylvian	3		3	
Trolard+Labbé+Sylvian	5		1	
	65		65	

TABLE IV
RELATIONSHIP OF HANDEDNESS, CEREBRAL DOMINANCE (WADA'S TEST), AND
PREDOMINANT SUPERFICIAL HEMISPHERIC VEINS

Case No.	Handedness	Cerebral Dominance (Wada's Test)	Right Hemisphere (vein)	Left Hemisphere (vein)
1	L	L	Trolard	Labbé
2	R and L	L	Trolard	Trolard, Labbé, Sylvian
3	L	R	Sylvian	Trolard
4	L	L	Trolard, Labbé	Labbé
5	R	L	Trolard, Labbé	Labbé
6	L	L		Trolard, Labbé, Sylvian
7	L	R	Labbé	Trolard, Labbé, Sylvian
8	R	L	Trolard, Labbé, Sylvian	Labbé
9	R	L	Trolard	
10	R	L		Labbé
11	R	L	Sylvian	Labbé
12	R	L		Labbé
13	R	L	Trolard, Labbé	Labbé
14	R	L	Trolard	
15	R	L	Trolard, Labbé	Trolard, Sylvian
16	R	L	Trolard	Labbé
17	R	L	Trolard	
18	R	L	Trolard, Sylvian	Labbé
19	R	L	Trolard, Labbé, Sylvian	Trolard
20	R and L	L	Trolard	Labbé
21	R	L		Labbé
22	R	L	Trolard, Labbé	
23	R	L		Trolard, Sylvian
24	R	L	Trolard	Labbé
25	R	L	Trolard, Labbé	Trolard, Labbé
26	R	L	Trolard, Labbé	Trolard, Labbé
27	R	L	Trolard	Labbé
28	L	R		Trolard
29	R and L	L	Trolard	Trolard, Labbé
30	R	L		Labbé, Sylvian
31	L	R	Labbé	Trolard, Labbé, Sylvian
32	R and L	R	Labbé	Trolard, Labbé, Sylvian
33	L	R	Trolard, Sylvian	Labbé
34	R and L	L	Labbé	Labbé
35	R	L	Labbé	Labbé, Sylvian
36	R	L		Labbé
37	R	L		Labbé
38	R	R	Labbé	Trolard
39	R	L		Labbé
40	L	L	Trolard	Trolard, Labbé, Sylvian
41	R and L	R	Labbé	Trolard
42	R	L	Sylvian	Sylvian
43	L	R	Labbé	Sylvian

at the level of the torcular Herophili is important. The right transverse sinus, the right sigmoid sinus and the right internal jugular vein contain blood derived mainly from the cortex and superficial parts of the

brain, while the left transverse sinus, the left sigmoid sinus and the left internal jugular vein contain blood mainly from the central and deep parts of the brain.

These observations have served as a basis

TABLE V
RELATIONSHIP OF RIGHT HEMISPHERIC DOMINANCE
AND SUPERFICIAL VENOUS PREDOMINANCE

Bilateral Angiography 8 cases		Unilateral Angiography 1 case	
R	L	R	L
S	TLS	—	T
L	TLS		
L	T		
L	T		
L	T		
L	TLS		
L	T		
T S	L		

T=vein of Trolard, L=vein of Labbé, and S=sylvian vein.

TABLE VI
RELATIONSHIP OF LEFT HEMISPHERIC DOMINANCE
AND SUPERFICIAL VENOUS PREDOMINANCE

Bilateral Angiography 21 cases		Unilateral Angiography 13 cases	
R	L	R	L
T	L	—	L
T	TLS	T	—
TL	L	—	L
TL	L	T	—
TLS	L	—	L
S	L	T	—
TL	L	—	L
TL	T S	TL	—
T	L	—	L
T S	L	—	L
TLS	T	—	T S
T	L	—	LS
T	L	—	TLS
TL	TL		
TL	TL		
T	L		
T	TL		
L	L		
L	LS		
T	TLS		
S	S		

T=vein of Trolard, L=vein of Labbé, and S=sylvian vein.

for practical therapeutic and diagnostic approaches. Because of the difference in behavior of the vessels at the level of the torcular Herophili, a "brain revascularization" operation consisting of the creation of a fistula between the common carotid and the jugular vein on the right was suggested by Beck and co-workers.¹ Certain differences in the results of the Queckenstedt maneuver, dependent on whether the compression is made on the right or left jugular vein, have been tentatively explained by this anatomic-functional peculiarity at the level of the torcular Herophili. The variations in symptoms caused by tumors blocking the venous drainage on one side or the other have also been ascribed by Gibbs⁶ to these differences at the level of the torcular Herophili.

Anatomic studies of Mannu,⁹ Testut,¹⁸ Edwards,² Padget¹⁴ and Woodhall²⁰ are in good agreement that the three most frequent arrangements of the sinuses at the torcular Herophili are: (1) *bifurcating sinuses*, encountered in about 50 per cent of the cases, in which both the superior and straight sinuses divide equally or unequally; (2) *unequal deviation*, encountered in 30 per cent of the cases, in which the superior longitudinal sinus leans to one side or the other and ends in either the left or, more frequently, the right transverse sinus; the straight sinus in these cases ends in the opposite transverse sinus, usually the left; (3) *unilateral deviation*, rare, in which both the superior longitudinal sinus and straight sinus deviate to one side and send slender communications to form the transverse sinus of the other side. In this type the greatest inequality in the size of the transverse sinuses is found. In a series of 100 normal sinograms, Morris¹⁰ obtained roentgenographic data comparable to the above mentioned anatomic findings. Nylin, Hedlund, and Regnström¹² in a recent study of the cerebral circulation with labelled red cells in normal subjects found that the injected erythrocytes were drained symmetrically through the two jugular bulbs after one carotid injection in 10 cases out of

TABLE VII
DRAINAGE FROM SUPERIOR LONGITUDINAL SINUS
AND SINUS RECTUS INTO RIGHT AND LEFT
TRANSVERSE SINUSES

Case No.	Right Carotid Injection		Left Carotid Injection	
	Right Transverse Sinus	Left Transverse Sinus	Right Transverse Sinus	Left Transverse Sinus
1	+	+	+	+
2	+	+	+	+
3	+	+	+	+
4	+	+	+	+
5	+	+	+	+
6	+	+	+	+
7	o	+	o	+
8	+	+	o	+
9	+	o	o	+
10	+	+	+	+
11	+	+	+	+
12	+	o	+	o
13	+	+	+	+
14	+	o	+	+
15	+	+	+	+
16	+	+	+	+
17	+	+	+	+
18	+	+	+	+
19	+	o	+	o
20	+	+	+	+
21	+	+	+	+
22	+	+	+	o
23	+	+	+	+
24	+	o	+	+
25	+	+	+	+
26	+	o	+	o
27	+	+	+	+
28	+	+	+	+
29	+	+	+	+
30	+	+	+	+
31	+	o	+	+
32	+	o	+	+
33	+	+	+	+
34	+	+	+	+
35	+	+	+	+

34 (29 per cent). In 8 cases (24 per cent) none or very slight activity was drained from the contralateral bulb after one carotid injection indicating that most of the injected labelled erythrocytes had passed through the ipsilateral jugular bulb.

Our observations were made from a series of 35 bilateral carotid angiographies in

which good filling of the superior longitudinal sinus, sinus rectus and transverse sinuses was obtained. The results are summarized in Table VII. In 24 cases (68.57 per cent) the contrast medium entered both the right and left transverse sinuses at the level of the torcular Herophili with approximate equal distribution, independent of the side injected (Fig. 16, *A* and *B*). In 4 cases (11.4 per cent) one of the transverse sinuses was dominant and received most of the medium from both hemispheres (Fig. 17, *A* and *B*). Of these 4 cases, 3 showed a right and one a left dominant sinus. In 1 case a complete lateralization of drainage was noted; the right transverse sinus received contrast material only from the right and the left sinus only from the left hemisphere. In 4 cases the medium entered the right transverse sinus from the right and both sinuses after left carotid injection. In 2 cases the opaque substance entered both sinuses after injection into the right carotid. The left injection produced filling of the left transverse sinus in 1 case and of the right in the other. By the use of oblique roentgenograms, it was possible in 1 case to demonstrate angiographically the discharge of the sinus rectus exclusively into the left transverse sinus (Fig. 18, *A* and *B*).

In the course of this study we were also able to confirm by angiography an ampullary dilatation at the point where the inferior longitudinal sinus and great vein of Galen fuse to form the straight sinus (Fig. 18*B*). This ampullary dilatation, not to be confused with the ampulla Galeni, has been described anatomically by Nikiforov¹¹ as "confluens sinuum anterior" as opposed to the posterior confluens, the torcular Herophili.

SUMMARY

Angiographic evidence is offered that the superficial cerebral veins are not situated "at random" but arranged according to determinate patterns. The three most important pathways of superficial venous drainage are the vein of Trolard, the superficial sylvian vein and the vein of Labbé. In



FIG. 16. Contrast medium entering from superior longitudinal and straight sinuses into both transverse sinuses after (A) right carotid and (B) left carotid injection.

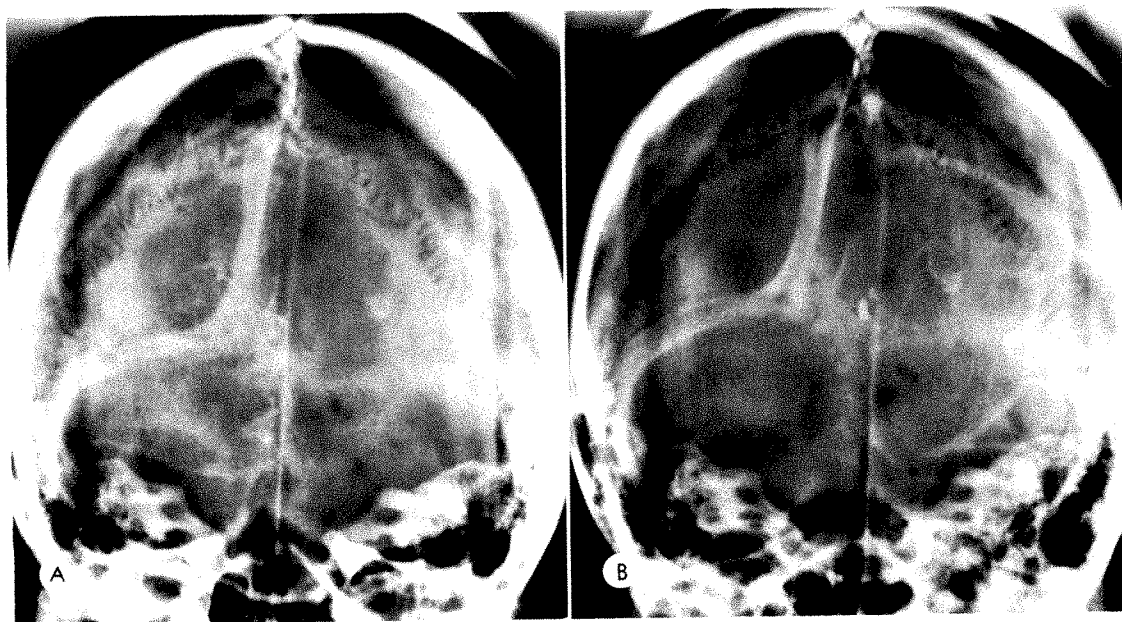


FIG. 17. Right transverse sinus receives contrast medium from both hemispheres after (A) right and (B) left carotid injection.

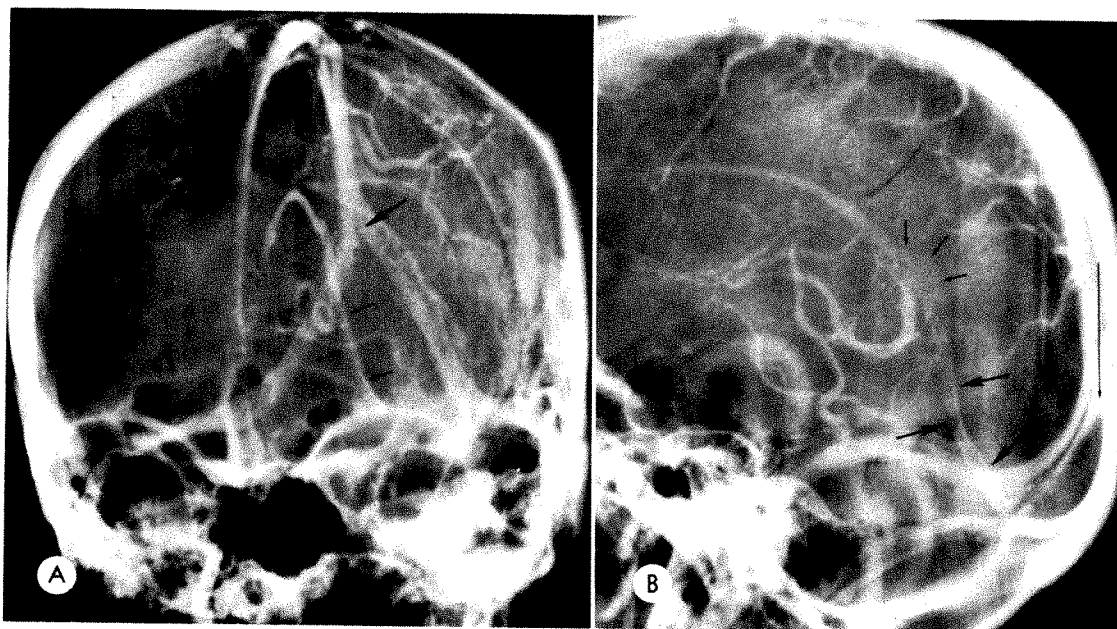


FIG. 18. (A) Straight sinus drains exclusively into left transverse sinus. Large arrow points to bifurcation of superior longitudinal sinus located considerably higher than usual. (B) Straight sinus drains exclusively into left transverse sinus (large arrows). Long arrow points to high bifurcation of superior longitudinal sinus. Small arrows outline ampullary dilatation: "confluens sinuum anterior."

the great majority of cases one of these three venous channels "predominates," *i.e.*, is larger than the others. Occasionally, two of these three channels, and only exceptionally all three, are of equal size.

The superficial venous discharge in the two hemispheres is generally different. In the present series the vein of Labbé predominates in the dominant hemisphere and the vein of Trolard in the nondominant hemisphere with a statistically significant incidence. The combination of Labbé's vein in the dominant and Trolard's vein in the nondominant hemispheres of each and the same patient also shows a statistically significant frequency.

Angiographic studies of the dural sinuses at the level of the torcular Herophili show that the blood from the superior longitudinal sinus and the sinus rectus enters in the majority of cases into the right and left transverse sinuses with approximately equal distribution. In a few cases, one of the transverse sinuses predominates and receives blood from both hemispheres;

rarely, the right transverse sinus receives blood only from the right and the left transverse sinus only from the left hemisphere. In exceptional cases it is possible to demonstrate angiographically that the blood from the deep brain, which is carried by the sinus rectus, discharges only into the left transverse sinus.

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The Wada tests were carried out by Drs. Edward Laskowski and Herbert Lansdell. Dr. Frank Macri offered valuable and constructive criticism. Mrs. Doris Sadowsky is responsible for the statistical analysis of the data.

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THE POSTERIOR INFERIOR CEREBELLAR ARTERY ON VERTEBRAL ANGIOGRAPHY*

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VERTEBRAL angiography has been an accepted procedure for several years,^{1,3,5,6,7,8} but has not as yet received the same amount of detailed attention as carotid angiography. It has been most useful in the diagnosis of aneurysms or arteriovenous anomalies in the posterior fossa as well as in the delineation of tumors with abnormal vasculature.^{2,4} The recognition, however, of tumors in the absence of a distinct stain on the basis of deviations or deformities of the normal cerebral vessels is frequently difficult because of many variations in the origin and distribution of these vessels. Variations in the course and distribution of the posterior inferior cerebellar artery are greater than those of the superior cerebellar artery. It is nevertheless possible to delineate a typical or standard configuration and area of supply for the posterior inferior cerebellar artery in both the lateral and anteroposterior projections (Fig. 1, *A* and *B*). The recognition of normal variations (Fig. 2, *A*, *B* and *C*; 3, *A*, *B* and *C*; and 4, *A* and *B*) and of pathologic deviations is simplified by comparison with this typical pattern.

The course of the posterior inferior cerebellar artery is intimately related to the adjacent structures which it supplies, specifically, the medulla, the inferior portion of the fourth ventricle, the inferior vermis, the tonsils and the inferior aspects of the cerebellar hemispheres. It is possible to localize these structures because of the characteristic configuration of the vessel in relationship to them. There are, however, also random features which are not directly determined by the anatomy of the brain stem and cerebellum. For example, the site of origin of the posterior inferior cerebellar

artery from the vertebral artery may vary from a point well below the level of the foramen magnum to the junction of the vertebral artery with the basilar artery. The course of the stem or first portion of the posterior inferior cerebellar artery will depend primarily on the site of origin. In the anteroposterior projection, the first portion of this vessel may be lateral or medial to the vertebral artery, depending on a high or a low take-off (Fig. 5). The sites of origin of the smaller branches of the posterior inferior cerebellar artery are also very variable. Branches to the same region may arise from different parts of the vessel.

The course of the posterior inferior cerebellar artery after its stem is conventionally described as forming a caudal loop followed by a cranial loop (Fig. 1*A*; 2, *A*, *B* and *C*; and 3, *A*, *B* and *C*). This description is primarily based on the appearance of the vessel in the lateral projection. These loops, however, can also be identified and similar terminology may be used when describing their appearance in the anteroposterior projection (Fig. 1*B*; 4, *A* and *B*; 5; and 6, *A*, *B* and *C*). The caudal loop curves around the medulla, often at the lower margin of the tonsil, to reach the region in front and medial to the tonsil where it lies on the inferior medullary velum, the roof of the fourth ventricle. Since the cranial loop follows immediately upon the caudal loop, they share a common limb which, in the diagrammatic representations (Fig. 1, *A* and *B*), has been designated as segment 2. The lowermost extent of the caudal loop or its apical portion may extend below the level of the foramen magnum. In some instances, this loop reaches well into the spinal canal along the side of the cord and

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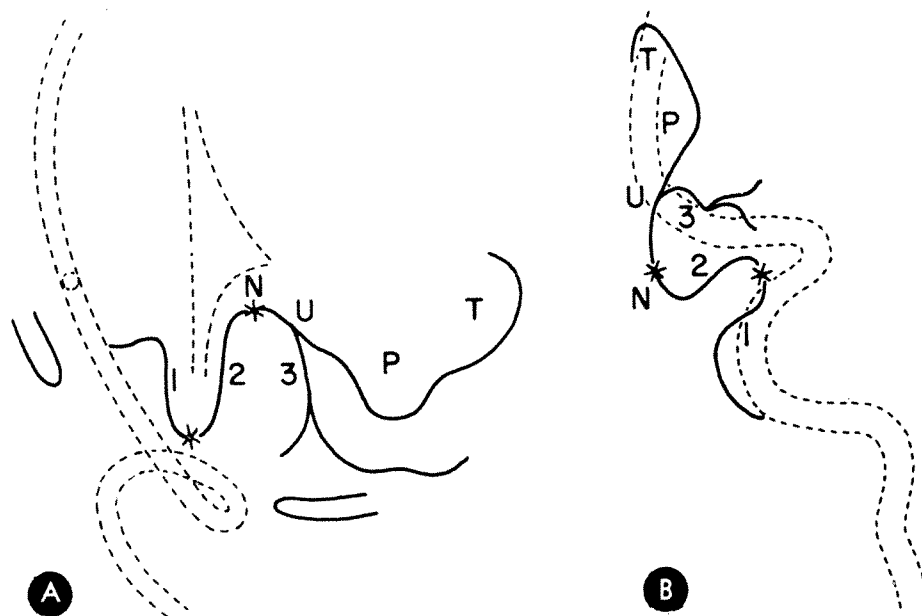


FIG. 1. (A) Diagrammatic representation of the typical appearance of the posterior inferior cerebellar artery in the lateral projection. After a variable origin, a caudal loop (segments 1 and 2) and a cranial loop (segments 2 and 3) are formed. Each loop may be said to consist of an anterior and a posterior limb with connecting segments or apices (asterisks). The posterior limb of the caudal loop and the anterior limb of the cranial loop are identical (segment 2). The main branches of the posterior inferior cerebellar artery usually arise a short distance distal to the apex of the cranial loop. The vermis branch runs posteriorly in the sulcus valliculae along the inferior aspect of the inferior vermis. The inferior vermis includes the nodulus (N) related to the roof of the fourth ventricle (dotted outline), the uvula (U), the pyramid (P), and the tuber (T). The tonsil may be said to lie roughly in the hollow of the cranial loop, that is, between segments 2 and 3. The vermis branch also forms a flat loop convex inferiorly with a local exaggeration in the region of the pyramid ("posterior loop"). The terminal portion of the vermis branch curves around the tuber in the posterior cerebellar notch. The tonsillo-hemispheric branch runs inferiorly near the posterior margin of the tonsil (prepyramidal sulcus), forming the posterior limb of the cranial loop (segment 3). Inferiorly this vessel gives off anterior or tonsillar branches and posterior or hemispheric branches which curve downwards and backwards around the biventral lobule to the under aspect of the cerebellar hemisphere.

(B) Diagrammatic representation of the typical configuration of the posterior inferior cerebellar artery in the half-axial anteroposterior projection. The designations correspond to those used in A. The first portion of the artery prior to the formation of the caudal loop is frequently obscured by the vertebral artery. Its course, medial or lateral to the vertebral artery, varies, depending on whether the take-off is low or high. The caudal loop, however, can be identified and must extend as far laterally as the lateral aspect of the medulla. The apex of the cranial loop is located close to the mid-line but may be 2 mm. to either side of the mid-line. The apices of the caudal and cranial loops in this projection correspond only approximately to the apices of the loops in the lateral projection. It is usually difficult to identify clearly the posterior limb of the cranial loop (segment 3), that is, the tonsillo-hemispheric branch. However, the posterior loop in the region of the pyramid (P) is easily recognizable by its typical laterally convex configuration. This lateral deviation of the posterior loop is due to the relatively greater width of the pyramid and its wings as compared to the adjacent portions of the vermis. The terminal portion of the vermis branch returns to the mid-line and turns around the tuber to extend forward on the superior aspect of the vermis. The opposite curvatures of the cranial and posterior loops in this projection create a characteristic S-shaped appearance. The relative sizes and relationships of the two portions of this S configuration depend on the exact angle of projection.

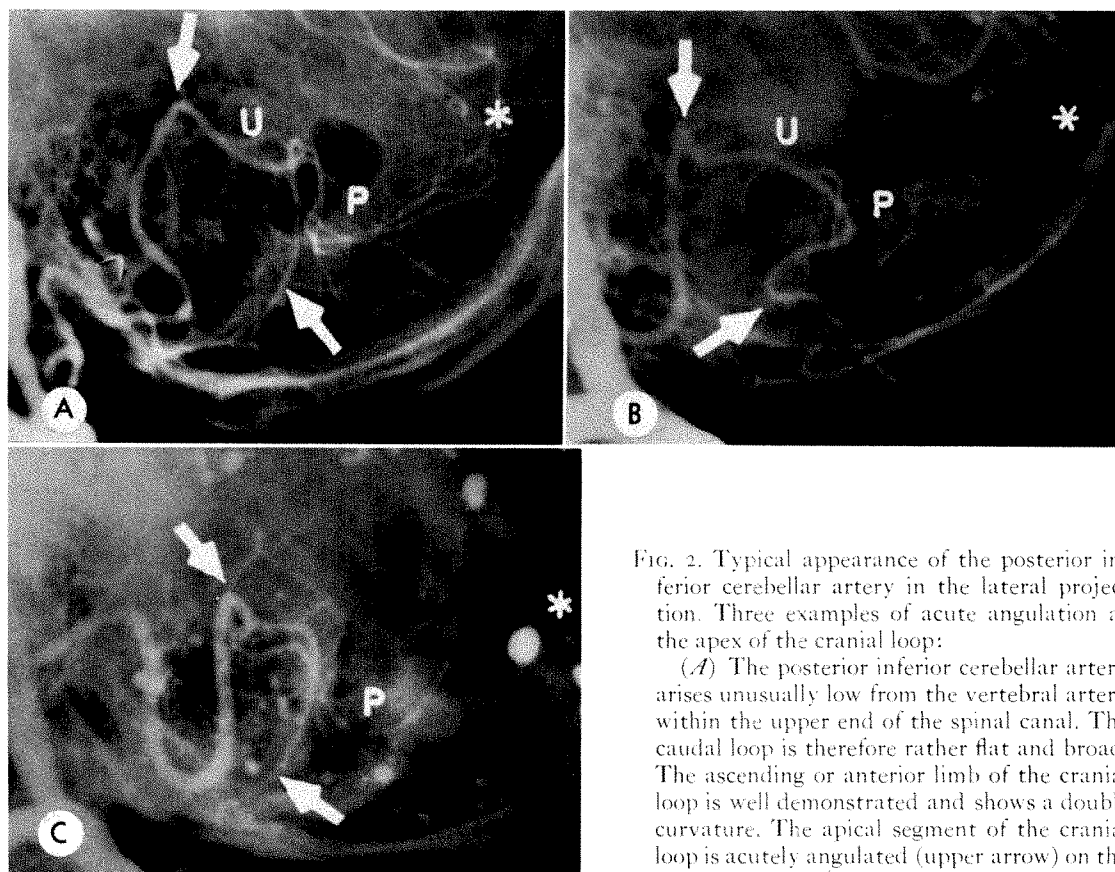


FIG. 2. Typical appearance of the posterior inferior cerebellar artery in the lateral projection. Three examples of acute angulation at the apex of the cranial loop:

(A) The posterior inferior cerebellar artery arises unusually low from the vertebral artery within the upper end of the spinal canal. The caudal loop is therefore rather flat and broad. The ascending or anterior limb of the cranial loop is well demonstrated and shows a double curvature. The apical segment of the cranial loop is acutely angulated (upper arrow) on the anterior limb and runs posteriorly with a moderate convexity inferiorly (U). The posterior

limb of the cranial loop, that is, the tonsillo-hemispheric branch (lower arrow) is relatively thin. Vermis branches extend posteriorly in a typical fashion with a localized inferior looping at the site of the pyramid (P). These branches turn around (asterisk) the tuber to anastomose on the superior surface of the vermis with branches of the superior cerebellar artery.

(B) The origin and the anterior limb of the caudal loop are obscured by the broad vertebral artery. The apex of the caudal loop descends to the level of the foramen magnum. The ascending limb of the cranial loop is vertical and straight. There is an acute angulation (upper arrow) at the junction of the anterior limb of the cranial loop with the apical segment. The apical segment extends posteriorly with a moderate convexity superiorly (U). The tonsillo-hemispheric branch (lower arrow) or the posterior limb of the cranial loop shows a tortuous course as it descends inferiorly to run along the under aspect of the cerebellar hemisphere. The vermis branch shows a typical configuration (P) and terminates (asterisk) in a loop which continues to run posteriorly on the medial aspect of the cerebellar hemisphere instead of turning forward over the tuber.

(C) The caudal loop is symmetric and smoothly curved. There is an acute angulation (upper arrow) of the anterior limb of the cranial loop with the apical or connecting segment which extends posteriorly almost horizontally. In addition, there is a short thin branch which arises from the apex (upper arrow) and extends further superiorly and posteriorly in the line of the anterior limb of the cranial loop. This branch extends as high as the apex or fastigium of the fourth ventricle. There is early division of the main stem into a relatively large tonsillar branch (lower arrow) and a typical vermis branch (P).

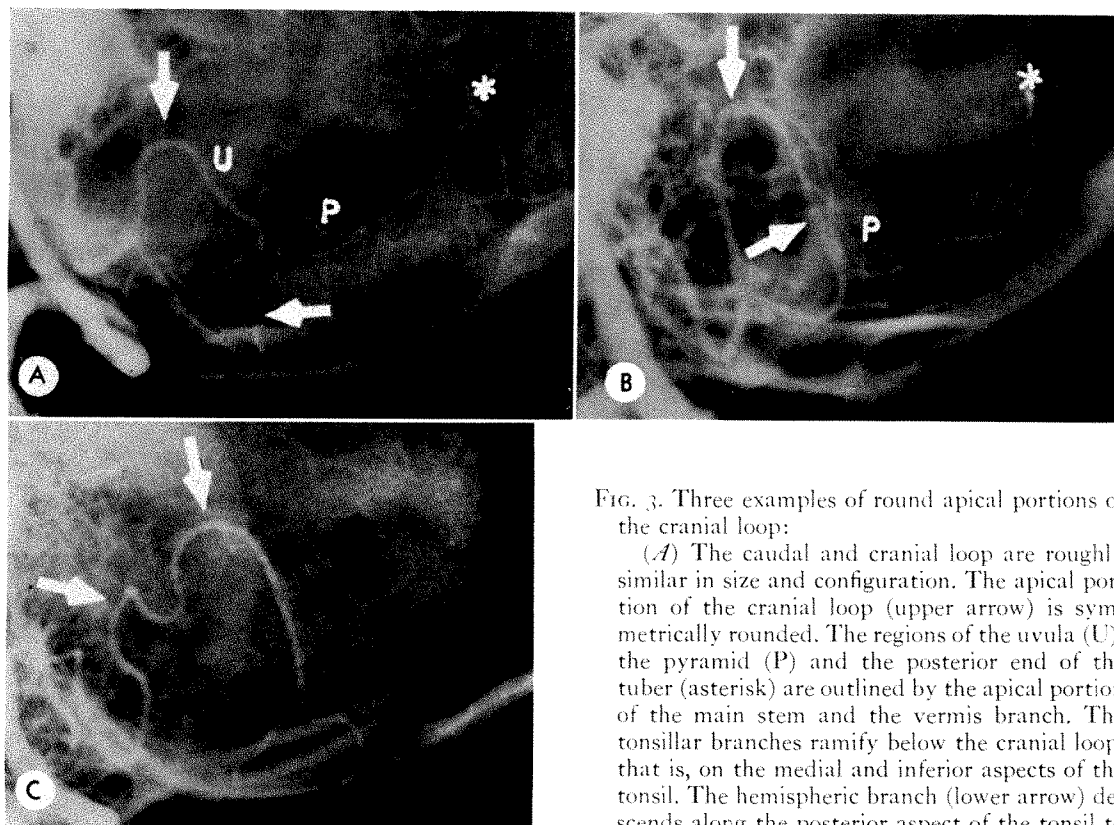


FIG. 3. Three examples of round apical portions of the cranial loop:

(A) The caudal and cranial loop are roughly similar in size and configuration. The apical portion of the cranial loop (upper arrow) is symmetrically rounded. The regions of the uvula (U), the pyramid (P) and the posterior end of the tuber (asterisk) are outlined by the apical portion of the main stem and the vermis branch. The tonsillar branches ramify below the cranial loop, that is, on the medial and inferior aspects of the tonsil. The hemispheric branch (lower arrow) descends along the posterior aspect of the tonsil to supply the inferior aspect of the hemisphere.

(B) The posterior inferior cerebellar artery shows a smoothly undulating course with a tall cranial loop which extends unusually far superiorly (upper arrow). The posterior limb of the cranial loop is formed by a large tonsillo-hemispheric branch (lower arrow). The vermis branch shows a typical posterior loop with local exaggeration at the site of the pyramid (P). The region of the tuber appears to be rather flat. Small terminal vermis branches can be seen (asterisk) extending both anteriorly and posteriorly.

(C) The cranial loop in this patient is unusually tall and wide. A small extra loop (lower arrow) is superimposed on the anterior limb. The apex of this cranial loop (upper arrow) is located unusually high and continues without any change in caliber into the posterior or descending limb. Vermis branches are not evident.

presents a narrow hairpin appearance. This course must be considered anomalous, since the lower portion of the loop does not correspond to the inferior margin of the tonsil. In cases of displacement of the caudal loop due to tonsillar herniation, the loop is said to be relatively wide. Because of these normal variations, however, the diagnostic features of tonsillar herniation are uncertain. In most instances, the apex of the caudal loop lies distinctly above the foramen magnum, has a rounded appearance, and corresponds fairly closely to the lower margin of the tonsil. In the antero-

posterior projection (Fig. 4, A and B; 5; and 6, A, B and C), the lateral extent of the caudal loop corresponds to the lateral aspect of the medulla. The height to which the anterior limb of the cranial loop (segment 2, Fig. 1A) reaches superiorly shows less variation than the distal extent of the caudal loop. The position of the apex of the cranial loop is determined by the site of attachment of the inferior medullary velum in the region of the nodulus. When this attachment is located laterally to the nodulus and the ~~caudal~~ portion of the inferior medullary ~~vein~~ is absent, the region

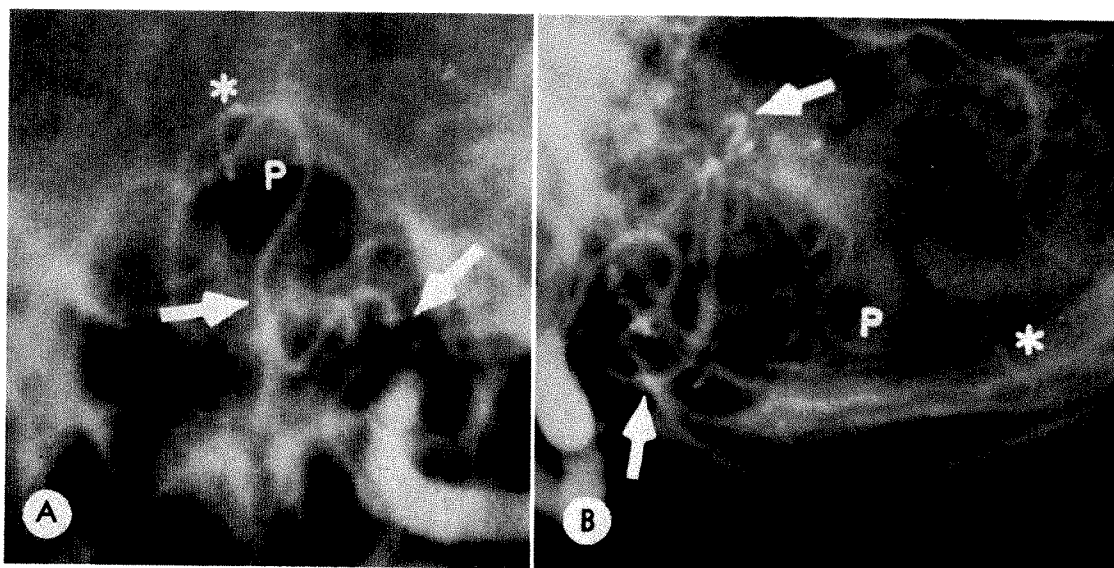
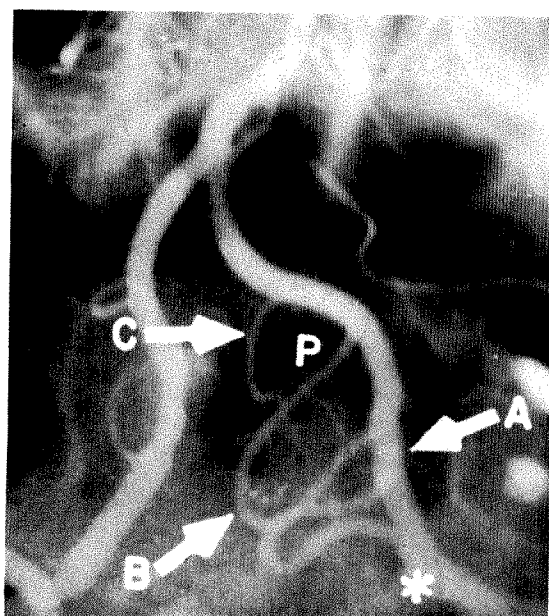


FIG. 4. (A) The posterior inferior cerebellar artery as seen in the half axial anteroposterior projection. The other cerebellar arteries were only poorly demonstrated, presumably because of technical difficulties in the performance of the injection. The lateral arrow marks the apex of the caudal loop, corresponding to the lateral aspect of the medulla. The medial arrow marks the apex of the cranial loop on the medial surface of the tonsil. In this case, there is no well-developed tonsillo-hemispheric branch and the posterior continuation of the cranial loop is directly into the vermis branch. This shows the typical lateral convexity or posterior loop in the region of the pyramid (P). Behind this area, the vessel returns to the mid-line in the region of the tuber (asterisk).

(B) The lateral projection in the same patient. The arrows mark the apices of the caudal and cranial loops. As on the anteroposterior roentgenogram, there is no evidence of a well-developed tonsillo-hemispheric branch. There is acute angulation at the junction of the anterior limb of the cranial loop with a tortuous apical or connecting segment. The vermis branch has a characteristic configuration (P) except for its posterior end (asterisk) which continues directly posteriorly to the internal occipital protuberance.



in the mid-line in front of the nodulus is not a free space and the artery cannot extend as high as the fastigium or apex of the fourth ventricle. In some instances, however, there is a free space between the central portion of the inferior medullary velum and the nodulus, and the apex of the cranial loop may extend to the fastigium.

FIG. 5. The position of the head in this projection resembles that seen in an anteroposterior Water's projection. The posterior inferior cerebellar artery arises rather low (asterisk) and runs medially before reversing itself and forming the caudal loop (arrow A). The apex of the cranial loop (arrow B) reaches the mid-line. The posterior or pyramid loop (P) is well seen and the terminal portion of the vermis branch returns to the mid-line and hooks (arrow C) over the tuber to run forward.

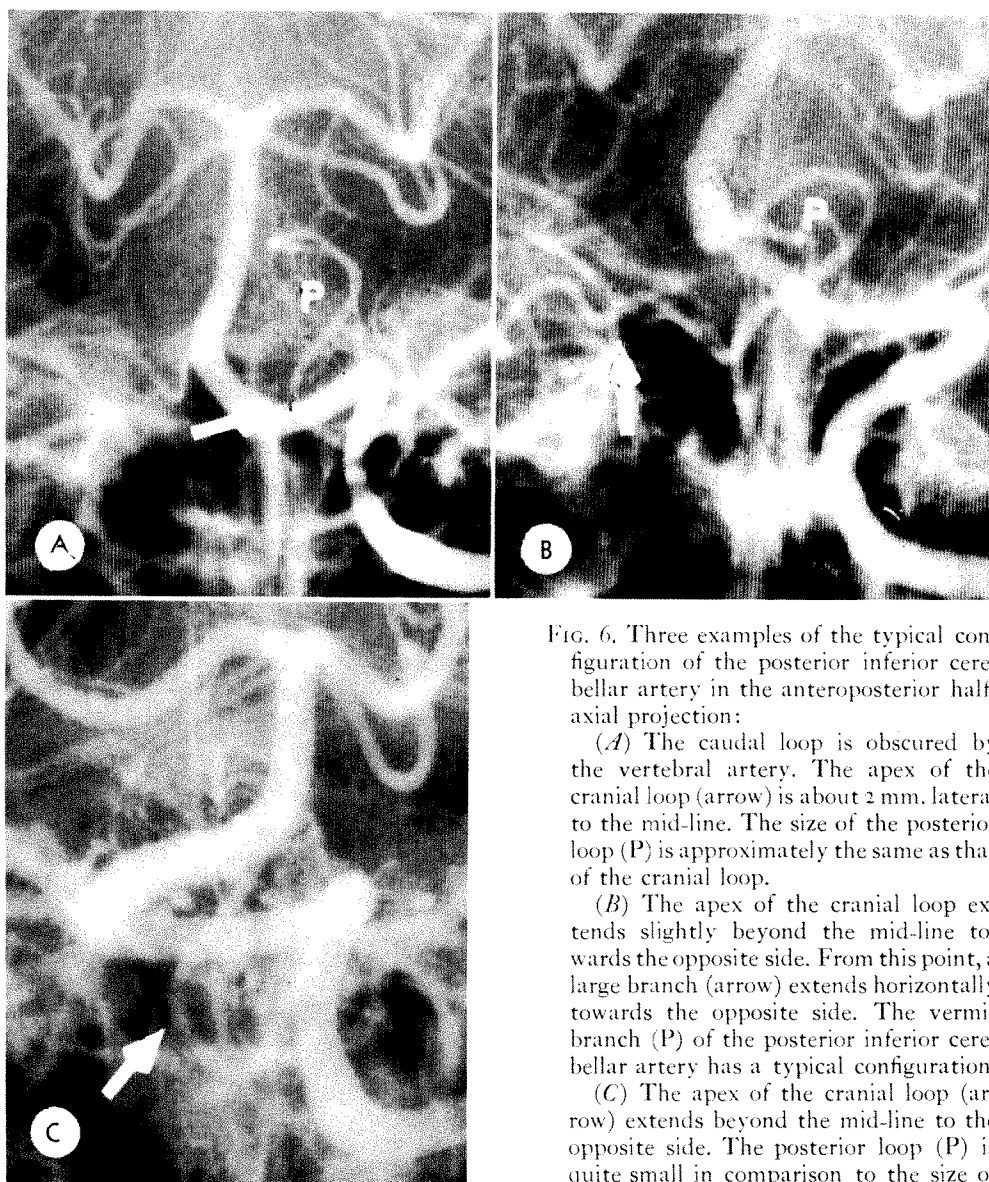


FIG. 6. Three examples of the typical configuration of the posterior inferior cerebellar artery in the anteroposterior half-axial projection:

(A) The caudal loop is obscured by the vertebral artery. The apex of the cranial loop (arrow) is about 2 mm. lateral to the mid-line. The size of the posterior loop (P) is approximately the same as that of the cranial loop.

(B) The apex of the cranial loop extends slightly beyond the mid-line towards the opposite side. From this point, a large branch (arrow) extends horizontally towards the opposite side. The vermis branch (P) of the posterior inferior cerebellar artery has a typical configuration.

(C) The apex of the cranial loop (arrow) extends beyond the mid-line to the opposite side. The posterior loop (P) is quite small in comparison to the size of the cranial loop but this is partly due to the angle of projection.

The apical or connecting portion of the cranial loop shows a somewhat variable configuration as seen in the lateral projection. There is often a rather acute angulation at the apex or at the junction of the anterior limb with the apical or transverse portion (Fig. 2, *A*, *B* and *C*). In other cases, however, the apical portion of the cranial loop shows a symmetric rounded configuration (Fig. 3, *A*, *B* and *C*). The apical portion of the posterior inferior cerebellar

artery is related to the uvula of the inferior vermis, and as it extends posteriorly may be straight or show a slight convexity superiorly or inferiorly. In the anteroposterior projection (Fig. 4, *A* and *B*; 5; and 6, *A*, *B* and *C*), the cranial loop is markedly convex towards the mid-line and in most cases its apex lies within a short distance, 1 or 2 mm. of the mid-line on one or the other side. The convexity of the cranial loop in the anteroposterior projec-

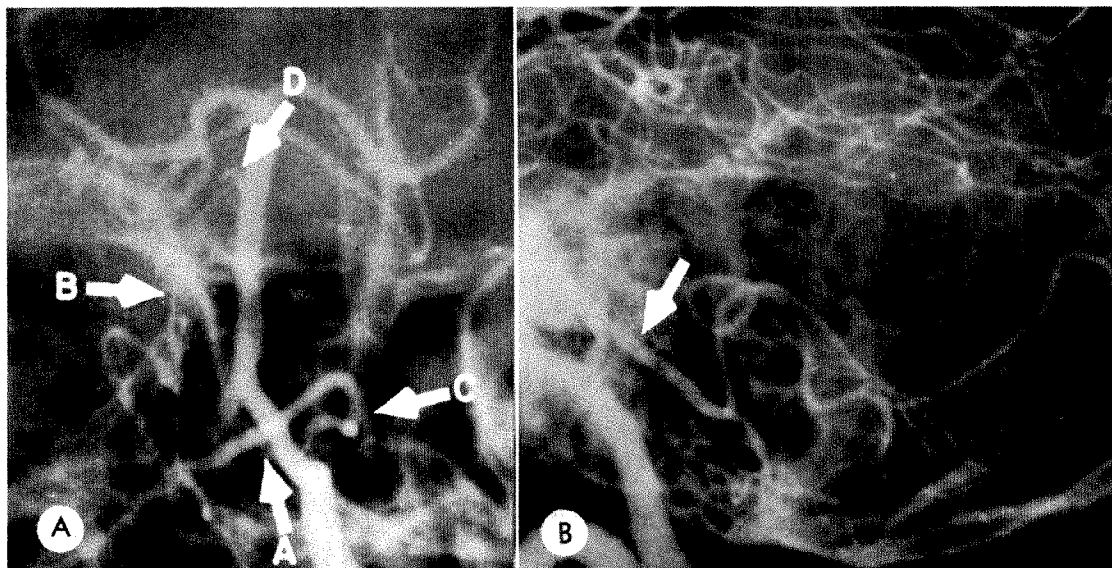


FIG. 7. Example of an expanding lesion in the left cerebellar hemisphere:

(A) The anteroposterior angiogram shows marked displacement of the posterior inferior cerebellar artery towards the right (arrows A and B). The caudal loop (arrow C) remains on the left side. The terminal portion (arrow D) of the displaced vermis branch returns to the mid-line, suggesting that the neoplasm is located anteriorly.

(B) In the lateral projection, there is little indication of the marked contralateral displacement. The cranial loop as well as its branches do not appear to be remarkable. The caudal loop, however, is straightened and elongated (arrow).

tion is due to the medial bulging of the tonsil into the vallecula. The fact that this portion of the posterior inferior cerebellar artery lies closely to the mid-line is very useful in the determination of lateral displacements. Slight displacement to the opposite side, however, is not necessarily abnormal. An evaluation of the significance of lateral displacement of this vessel (Fig. 7, A and B; and 8, A and B) must also depend on the configuration of the vessel as well. True lateral displacement is associated with flattening or reversal of the normal medial convexity of the cranial loop.

In the majority of cases, the branching of the posterior inferior cerebellar artery into its two main terminal branches, namely, the vermis branch and the tonsillo-hemispheric branch, occurs a short distance beyond the apex of the cranial loop. These branches are often not of identical size. One or the other may be the larger and appear as a direct communication of the main channel. When the tonsillo-hemispheric branch is

the larger channel, the cranial loop is complete since it is this branch which forms the posterior or descending limb of this loop. The tonsillo-hemispheric branch descends approximately along the posterior margin of the medial aspect of the tonsil and divides into tonsillar branches which extend anteriorly and hemispheric branches which extend downwards and posteriorly. The hemispheric branches as they turn around the biventral lobule to run on the under aspect of the cerebellar hemisphere are frequently so close to the occipital bone that they are obscured. In the anteroposterior projection, the tonsillo-hemispheric branch is frequently difficult to identify and, as a result, the cranial loop in this projection is often incomplete (Fig. 4, A and B). In this projection, small branches to the inferior aspects of the tonsils and cerebellar hemispheres may be seen arising from the stem or from the caudal loop of the posterior inferior cerebellar artery.

The vermis branch of the posterior infe-

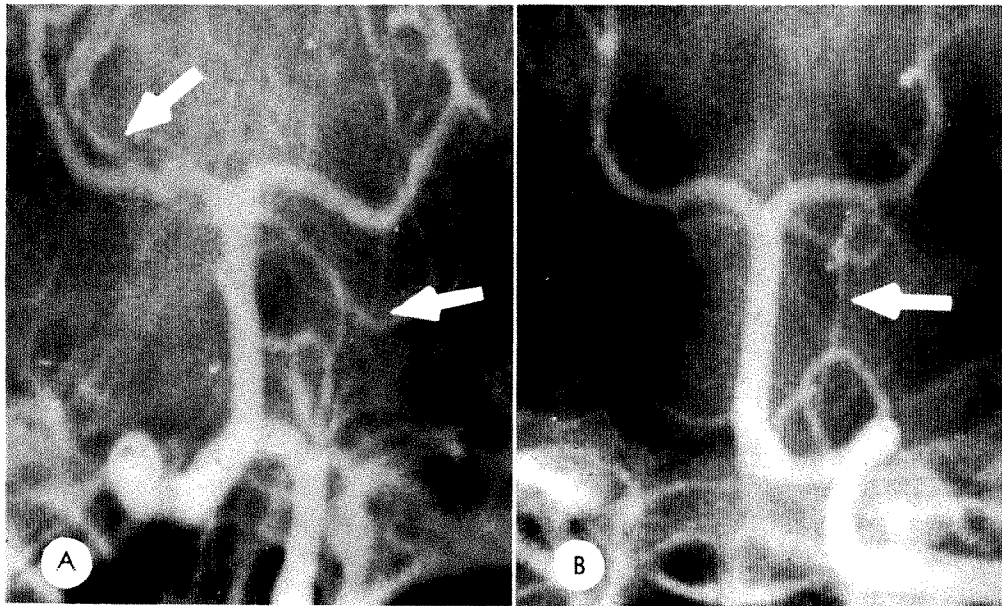


FIG. 8. Two examples of displacement of the posterior inferior cerebellar artery towards the injected side:

(A) This patient had a recurrent tumor of the right cerebellar hemisphere. The injection was done in the left vertebral artery and the left posterior inferior cerebellar artery was filled. This is clearly displaced towards the left side and shows a convexity (lower arrow) towards the left as well. The normal S-shaped configuration of the posterior inferior cerebellar artery is effaced. Incidentally, there is also elevation and flattening of the right superior cerebellar artery (upper arrow).

(B) A similar case showing displacement of the homolateral posterior inferior cerebellar artery. The displacement and flattening are most marked posteriorly (arrow), that is, in the vermis branch. A tumor involving the vermis was found at operation.

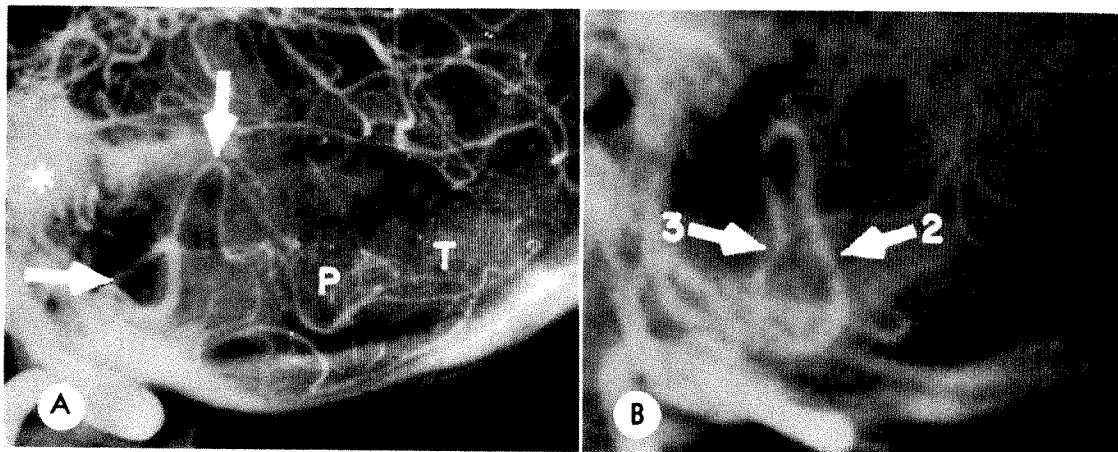


FIG. 9. Two examples of very narrow cranial loops:

(A) The cranial loop (upper arrow) is quite narrow and the vermis branch is undulating in configuration. However, the inferior looping due to the pyramid (P) and the course around the tuber (T) are evident. A large recurrent tonsillar branch arises from the ascending limb of the cranial loop (lower arrow). In addition, there is a tortuous communicating vessel (asterisk) between the superior cerebellar and the inferior cerebellar arteries.

(B) The cranial loop is narrow and the limbs of this loop are reversed, that is, the more posteriorly located limb (segment 2) is more proximally located than the anterior limb (segment 3). The vermis and tonsillo-hemispheric branches come off the lower part of the more distal, more anteriorly located limb and show atypical courses as they extend posteriorly.

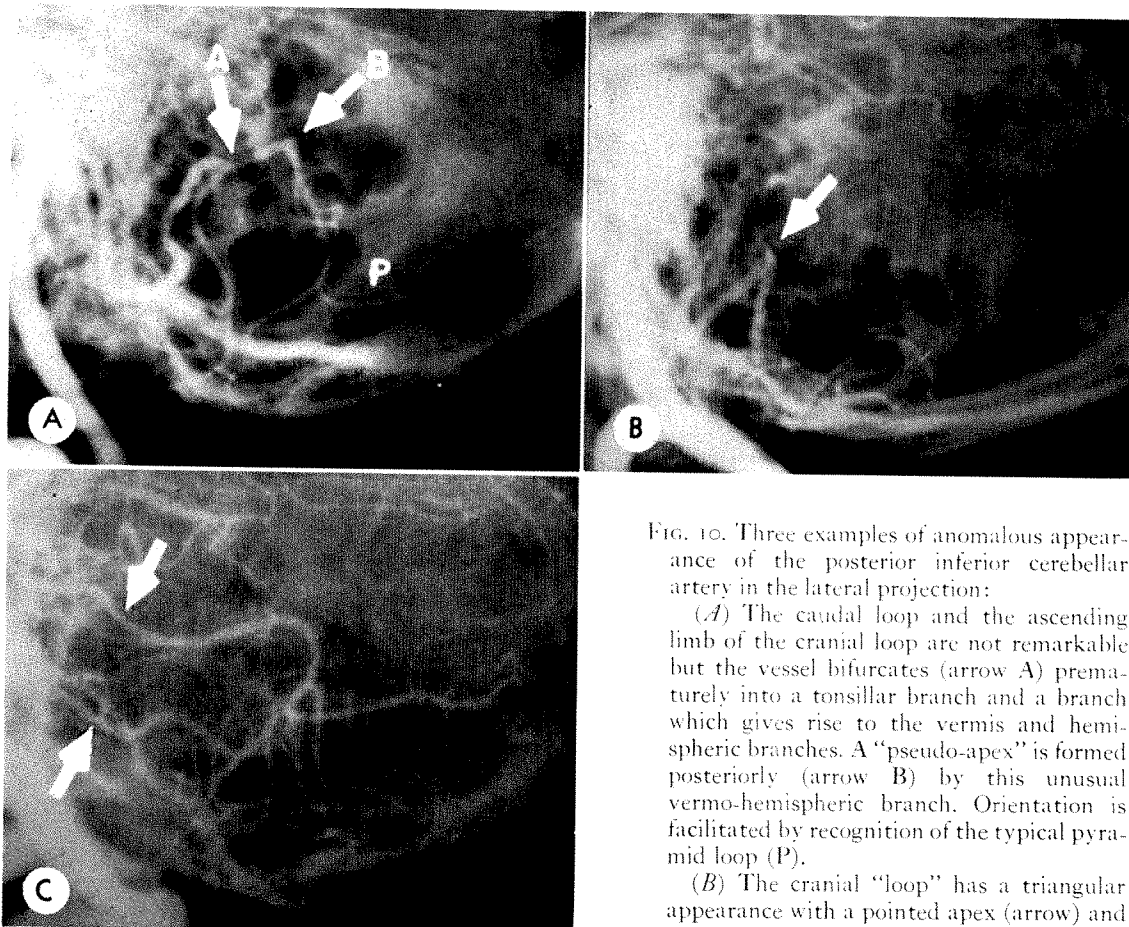


FIG. 10. Three examples of anomalous appearance of the posterior inferior cerebellar artery in the lateral projection:

(A) The caudal loop and the ascending limb of the cranial loop are not remarkable but the vessel bifurcates (arrow A) prematurely into a tonsillar branch and a branch which gives rise to the vermis and hemispheric branches. A "pseudo-apex" is formed posteriorly (arrow B) by this unusual vermo-hemispheric branch. Orientation is facilitated by recognition of the typical pyramid loop (P).

(B) The cranial "loop" has a triangular appearance with a pointed apex (arrow) and is quite low in position. A thin branch con-

tinues to run upwards from the apex and becomes the vermis branch. The main channel continues as the hemispheric branch.

(C) The posterior inferior cerebellar artery as such is not evident and appears to be absent. However, transverse vessels (arrows) arising from the basilar artery send branches to the regions ordinarily supplied by the posterior inferior cerebellar artery. In other words, anterior inferior cerebellar arteries replace the posterior inferior cerebellar artery in this case.

rior cerebellar artery shows a considerably more characteristic course in both the lateral and anteroposterior projections than the tonsillo-hemispheric branch. It runs on the under aspect of the inferior vermis or in the sulcus valliculae between the inferior vermis and the cerebellar hemisphere. In this location, the vermis branch also forms a loop, convex inferiorly and laterally—the "posterior" loop. In the region of the pyramid in both projections, there is a unique local exaggeration of this loop due to the fact that the pyramid and its wings form a wider and thicker structure than the other portions of the inferior vermis.

In contrast to the medial convexity of the cranial loop, the posterior loop is convex laterally. The combination of these two loops forms a characteristic S-shaped configuration in the anteroposterior projection (Fig. 4, A and B; 5; and 6, A, B and C). However, the relative size of these loops as well as their specific configuration in this view depends a great deal on the exact angle of projection. Since the inferior vermis does not extend as far posteriorly as the cerebellar hemispheres because of the posterior cerebellar notch, the termination of the vermis branch as it turns around the tuber is normally at some distance from the

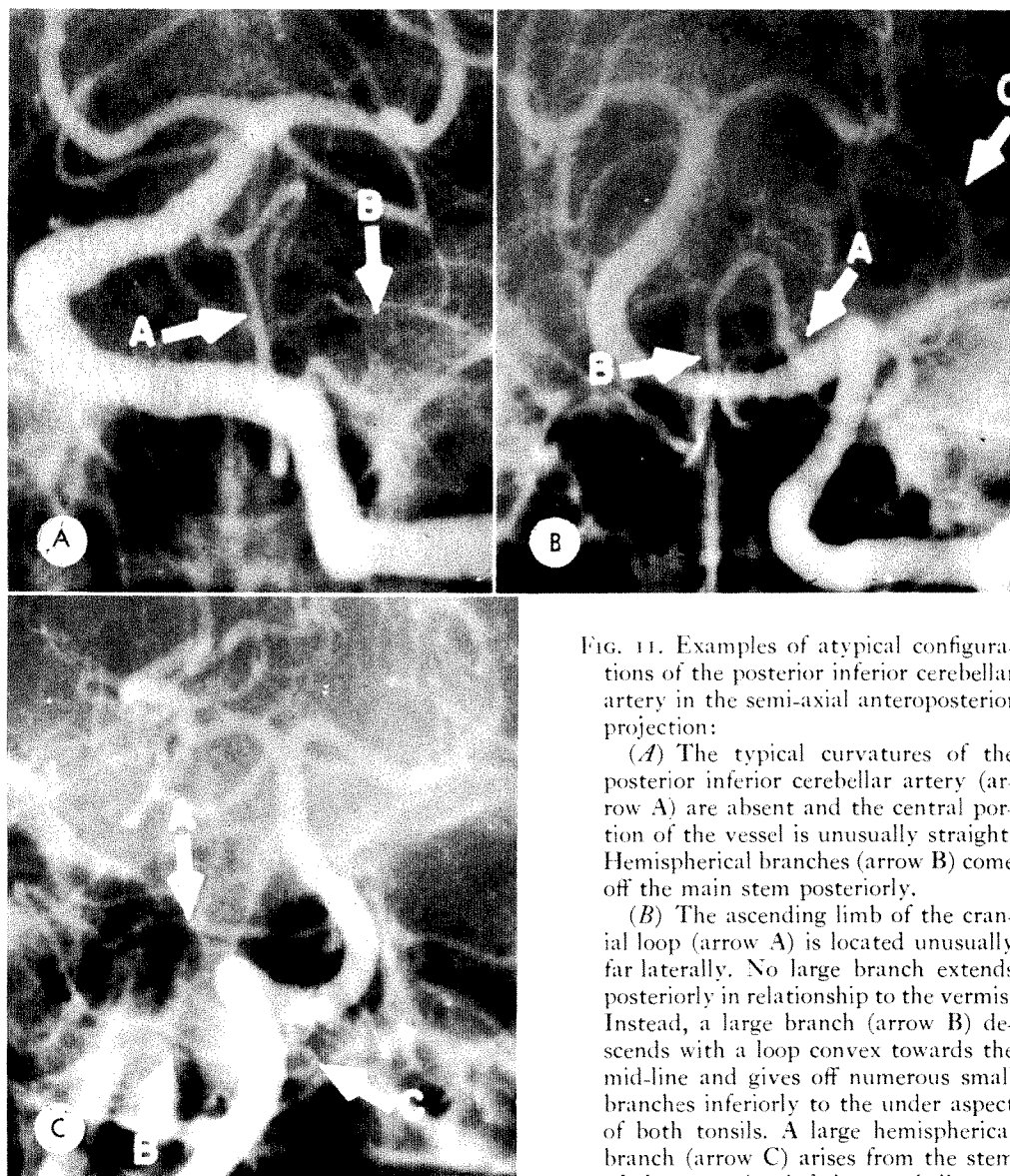


FIG. 11. Examples of atypical configurations of the posterior inferior cerebellar artery in the semi-axial anteroposterior projection:

(A) The typical curvatures of the posterior inferior cerebellar artery (arrow A) are absent and the central portion of the vessel is unusually straight. Hemispherical branches (arrow B) come off the main stem posteriorly.

(B) The ascending limb of the cranial loop (arrow A) is located unusually far laterally. No large branch extends posteriorly in relationship to the vermis. Instead, a large branch (arrow B) descends with a loop convex towards the mid-line and gives off numerous small branches inferiorly to the under aspect of both tonsils. A large hemispherical branch (arrow C) arises from the stem of the posterior inferior cerebellar artery.

tery. In the lateral projection in this patient (not demonstrated), the cranial loop was thin and pointed, resembling the configuration shown in Figure 10B.

(C) A transverse loop is formed between the anterior inferior cerebellar artery (arrow A) and the posterior inferior cerebellar artery (arrows B and C). This anastomotic branch of the posterior inferior cerebellar artery is located on the anterior aspect of the medulla and cerebellar hemisphere and is distinct from the posteriorly directed branches.

internal occipital protuberance. The terminal branches of the vermis artery are frequently multiple, some going over the superior aspect of the tuber to anastomose with the branches of the superior cerebellar artery (Fig. 2A), while others continue posteriorly on the medial aspect of the

cerebellar hemisphere (Fig. 2B). In the lateral projection, the terminal portion of this vessel usually shows a loop convex posteriorly (Fig. 2A). In the anteroposterior projection, this portion of the vermis branch is in the mid-line (Fig. 4A). The small twigs given off from its termination

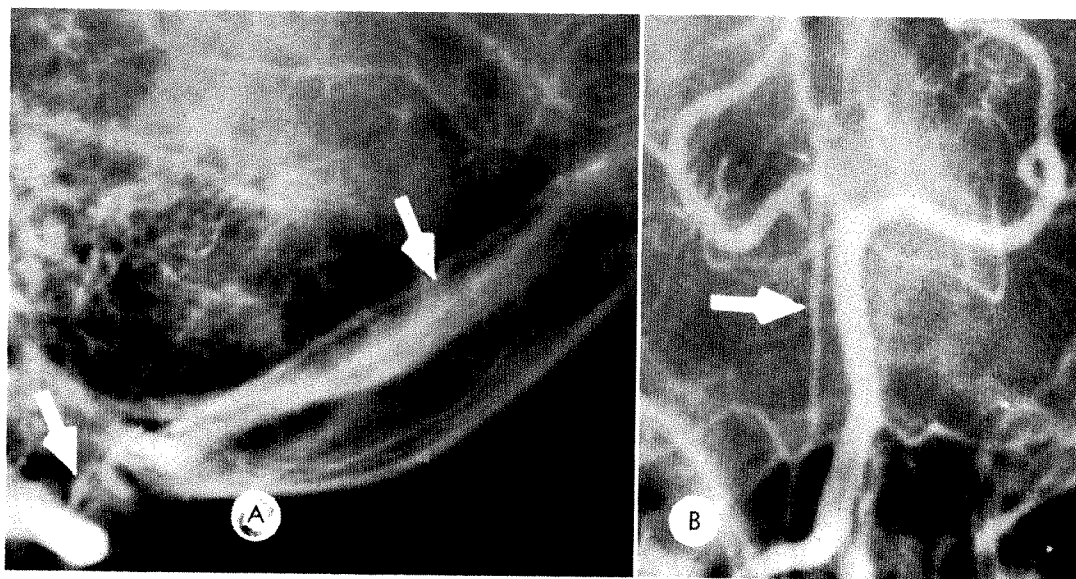


FIG. 12. Examples of a large posterior meningeal branch of the vertebral artery:

(A) The lateral angiogram shows the origin (lower arrow) of the meningeal branch and its course through the foramen magnum and along the floor (upper arrow) of the posterior fossa to the internal occipital protuberance.

(B) The posterior meningeal branch of the vertebral artery as seen in the anteroposterior projection is in or immediately adjacent to the mid-line (arrow). It is considerably straighter than the posterior inferior cerebellar artery.

may, however, extend posteriorly and laterally, on the medial inferior aspect of the cerebellar hemisphere.

As already noted, there are numerous variations from the typical course and configuration of the posterior inferior cerebellar artery (Fig. 9, A and B; 10, A, B and C; and 11, A, B and C). In some cases the cranial loop is quite narrow (Fig. 9A) and occasionally the relationship of the limbs of this loop is reversed (Fig. 9B). In other cases, the posterior inferior cerebellar artery fails to give rise to any significant vermis branch but supplies only the tonsil and the inferior aspect of the cerebellar hemisphere (Fig. 10B; and 11B). In such instances, vermis branches may arise from anterior inferior or superior cerebellar vessels. Anastomoses between the anterior inferior cerebellar vessels and the posterior inferior cerebellar arteries are not unusual. In some instances, there is no evidence of any posterior inferior cerebellar artery and both tonsillar and vermis branches arise from anterior inferior or superior cerebellar ves-

sels (Fig. 10C). It is not uncommon for the posterior inferior cerebellar artery of one side to give branches to the opposite tonsil (Fig. 6B). In fact, the posterior inferior cerebellar artery on one side may be completely replaced by a branch from the opposite posterior inferior cerebellar artery. In this connection, it might be noted that only one posterior inferior cerebellar artery will ordinarily be filled in the course of vertebral angiography. This has some advantage in the interpretation of the lateral angiogram because of absence of superimposition. In the anteroposterior projection, however, comparison between the two sides may not be possible. Vertebral angiography should therefore preferably be done on the side of the suspected lesion. However, since both posterior inferior cerebellar arteries often show similar displacements, it is possible to draw similar conclusions from one or the other (Fig. 8, A and B). A confusing factor in the recognition of the posterior inferior cerebellar artery in the anteroposterior projection is the visualization of a

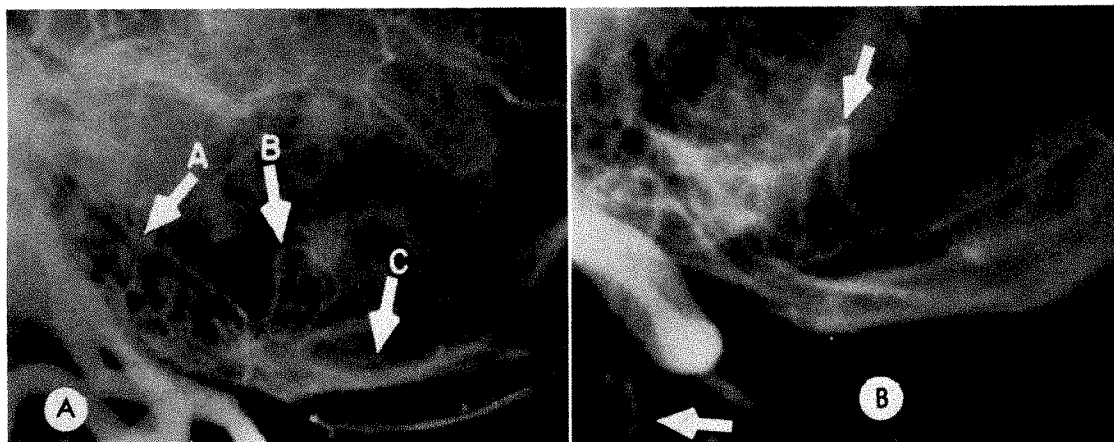


FIG. 13. Two examples of downward and posterior displacement of the posterior inferior cerebellar artery:

(A) The configuration of the posterior inferior cerebellar artery shows a markedly abnormal appearance. The apex of the cranial loop (arrow B) is displaced posteriorly as well as inferiorly. The segment of the vessel anterior to the cranial loop (arrow A) is elongated and markedly stretched. The vermis branch (arrow C) is displaced towards the floor of the posterior fossa. These changes were the result of a tentorial meningioma which compressed the fourth ventricle from above.

(B) The cranial loop is displaced downward and backward (upper arrow). The vermis branch is moderately displaced towards the base of the skull. A markedly elongated hairpin loop (lower arrow) extends down into the spinal canal. The appearance of this loop, however, is not necessarily abnormal. A tentorial meningioma was found in this patient.

rather constant posterior meningeal artery (Fig. 12, *A* and *B*) which arises from the vertebral artery near the foramen magnum and runs posteriorly and upwards in or near the mid-line adjacent to the bone. In contrast to the posterior inferior cerebellar artery, this vessel has a straight, sometimes finely undulating, course which, combined with its characteristic location in the lateral projection, serves to distinguish it from the posterior inferior cerebellar artery.

As pointed out above, displacements of the posterior inferior cerebellar artery away from the mid-line can ordinarily be recognized on a suitable anteroposterior angiogram. The side of an expanding lesion can thereby be determined (Fig. 7, *A* and *B*; and 8, *A* and *B*). Occasionally, displacement may be confined or maximal in either the anterior or posterior portion of the vessel, suggesting anteroposterior localization as well. However, such anteroposterior localization is difficult and may be equivocal if asymmetric tonsillar herniation should be present. The lateral angiogram is more suitable for the recognition of antero-

posterior displacement and is most useful in the recognition of downward dislocation. The most common type of displacement of this vessel is downwards and backwards (Fig. 13, *A* and *B*), due to tumors in the region of the tentorial notch or upper brain stem or as a result of tentorial herniation. Such displacement is most clearly seen by observation of the position and configuration of the cranial loop. The apex of the loop is located unusually far posteriorly and is unusually low in position. The cranial loop is also narrowed and tilted posteriorly with its anterior limb flattened and stretched posteriorly. The caudal loop may also be stretched and partially effaced. Forward (Fig. 14) or forward and downward displacement of the posterior inferior cerebellar artery occurs as a result of tumors in the posterior portion of the cerebellum. In such instances, the apex of the cranial loop appears displaced forward and the posteriorly directed branches are flattened or stretched. Downward displacement of the apical portion of the cranial loop is usually combined with downward

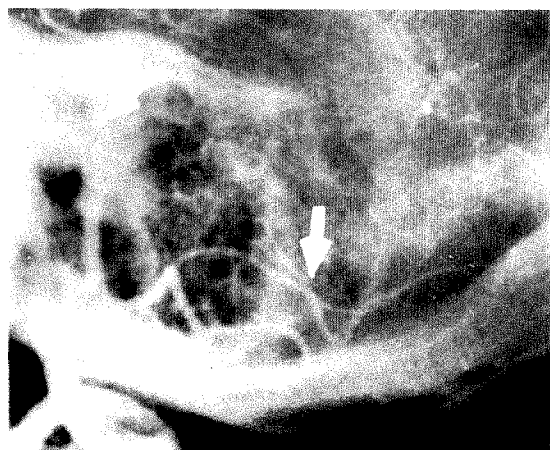


FIG. 14. An example of anterior displacement of the cranial loop. The cranial loop and its posterior limb (upper arrow) are displaced in a forward direction. The cranial loop is obscured by overlying bone but is presumably narrowed. The posterior branches are elongated and flattened (lower arrow). These changes were the result of a metastatic lesion in the cerebellar hemisphere from a carcinoma of the sigmoid.

displacement of the vermis branch (Fig. 15). Since the hemispheric branches can hardly be displaced inferiorly, downward displacement of the vermis branches results in a diminution in the distance between the vermis and the hemispherical branches as seen in the lateral projection. In such cases,

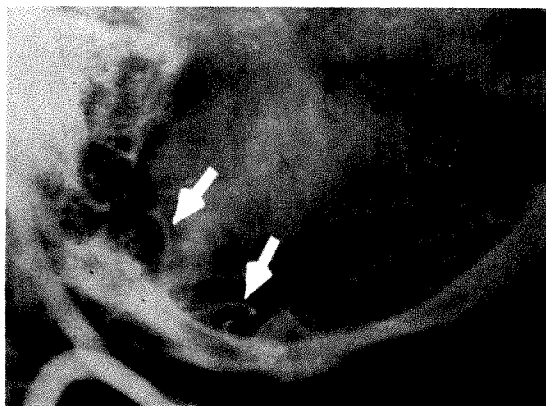


FIG. 15. An example of marked downward and forward displacement of the posterior inferior cerebellar artery. The posterior inferior cerebellar artery (arrows) is so markedly displaced downwards that much of it is obscured by the bony margins of the foramen magnum. At operation, a hemangioblastoma was found in the cerebellar hemisphere.

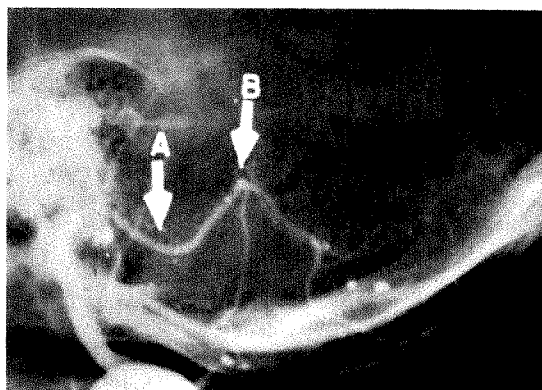


FIG. 16. Tumor of the brain stem in a child. The apex of the cranial loop (arrow B) is displaced backwards. In addition, the caudal loop (arrow A) is flattened and stretched.

it may be difficult to distinguish between these two sets of branches. Upward displacement of the posterior inferior cerebellar artery is rare since few tumors occur below this vessel. The general angiographic principle—that a localized deformity of a portion of the vessel is likely to be associated with a tumor in its immediate neighborhood while a more generalized displacement is more likely to be the result of a distant expanding process—also applies to the interpretation of abnormalities in the configuration of the posterior inferior cerebellar artery (Fig. 16; and 17, A and B).

Displacements of the posterior inferior cerebellar artery in the lateral projection can frequently be determined by simple visual inspection which effectively combines displacement with changes in configuration. In some cases, however, displacement is not obvious, particularly if deformity of the vessel is not present. It would be convenient if a semi-quantitative estimate of the normal location of some part of this vessel could be devised. An attempt was made, in a group of presumably normal cases, to determine the relationship of the apex or highest point of the cranial loop to Twining's line. This line was chosen because of its well known usefulness in determining the position of the fourth ventricle. This line is drawn from the tuberculum sellae to the internal occipital

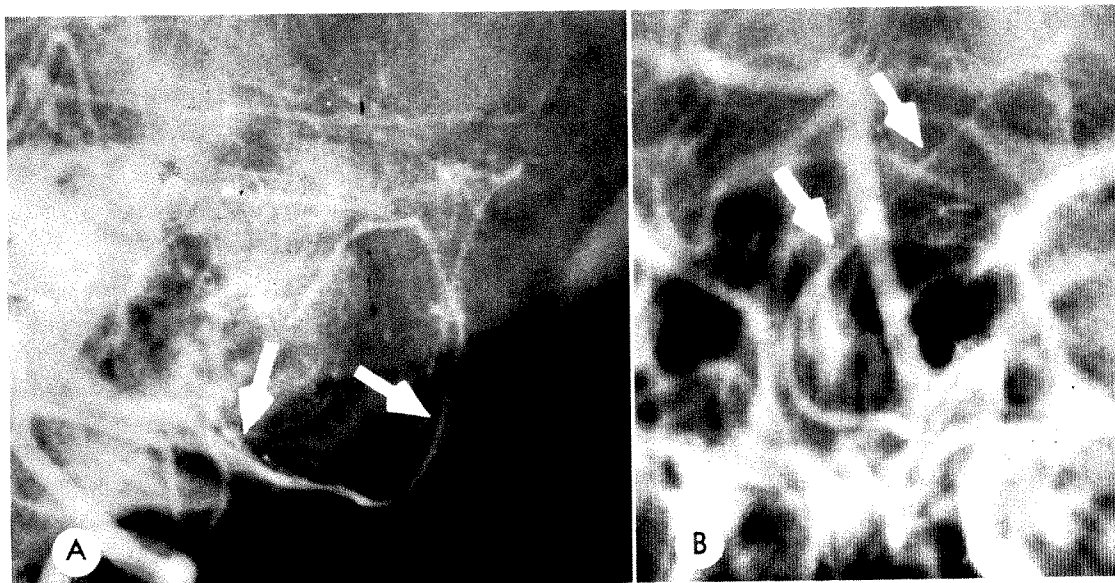


FIG. 17. Recurrence of a posterior fossa tumor:

(A) There is extreme flattening and elongation of the posterior inferior cerebellar artery (arrows) which extends into the suboccipital decompression.

(B) In the anteroposterior projection, only the posterior portion (arrows) of the posterior inferior cerebellar artery is elongated, straightened and deviated towards the left.

protuberance. It is, however, not always easy to identify the internal occipital protuberance. A more useful point⁹ is the lower margin of the groove for the transverse sinus as projected in the area of the occipital protuberance. Since both transverse sinuses are projected close to each other, a point midway between the lower margin of each was taken to represent the "internal occipital protuberance" or the posterior termination of Twining's line. There appeared to be no useful relationship between the distance from the apex of the cranial loop to Twining's line as measured along a perpendicular line dropped from the apex to this line. However, if one draws a line parallel to Twining's line through the lower margin of the internal auditory meatus, the apex of the cranial loop is rarely below this "auditory line" by more than a millimeter. This relationship can be therefore used as an approximate indication in a superoinferior direction of the normal position of the apex of the cranial loop. In order to determine the anteroposterior position, the distance from the foot of the perpen-

dicular onto Twining's line to the tuberculum sellae was measured and expressed as a percentage of the complete length of Twining's line, that is, the distance from the tuberculum sellae to the occipital point (Fig. 18, A and B). This ratio varied from 53 to 59 per cent with an occasional case, apparently normal, being 52 or 60 per cent. In those individuals with a broad cranial loop which extended unusually high, the ratio was usually at the upper limit of this range while in those with a more acute angulation in the cranial loop or a lower position, the ratio was ordinarily in the lower range. It is simple to devise a proportional ruler which can be directly applied to the roentgenogram to determine whether the ratio deviates from an average figure of, for example, 56 per cent (Fig. 19). Despite the fact that the range of normal is considerable, this measurement has been a useful approach to the recognition of displacements in an anteroposterior direction of the apex of the cranial loop. It should not be applied, however, to obviously anomalous vessels which show no true cranial

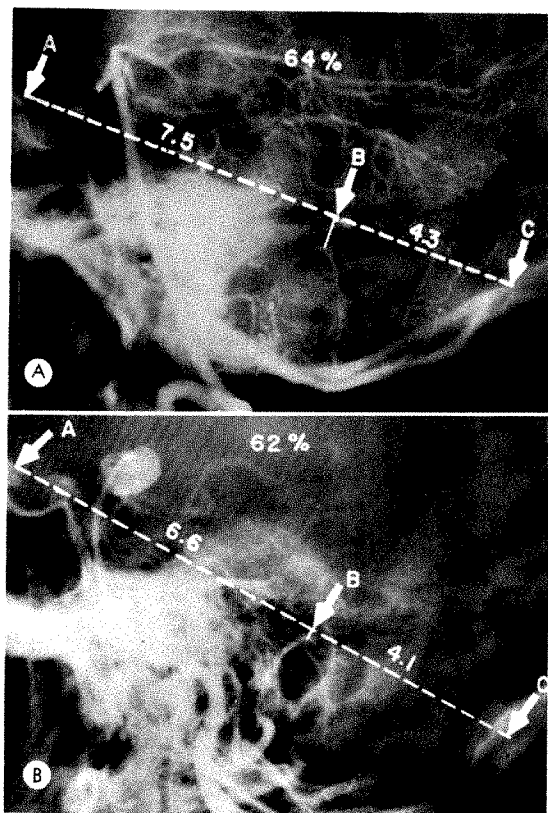


FIG. 18. Localization of the apex of the cranial loop:

(A) Twining's line is drawn from the tuberculum sellae (A) to the internal occipital protuberance or, rather, the lower margin of the groove due to the transverse sinus (C). A perpendicular line is drawn from the apex of the cranial loop to Twining's line (B). The ratio of the distance from the foot of the perpendicular to the tuberculum sellae to the total length of Twining's line, that is, the ratio of AB to AC is expressed as a percentage. In this patient, this ratio is 64 per cent, well above the upper limit of the normal range. A meningioma in the region of the tentorium and petrous pyramid was found at operation.

(B) The ratio of the distance from the foot of the perpendicular to the tuberculum sellae (AB) to the entire length of Twining's line (AC) in this patient is 62 per cent. This was due to an aneurysm at the bifurcation of the basilar artery, also demonstrated on this roentgenogram. Here, as in A, there is no remarkable deformity in the configuration of the posterior inferior cerebellar artery. It is difficult therefore to recognize posterior displacement by simple visual observation. In those instances with an acute angulation of the cranial loop, such as those demonstrated in Fig. 2, A, B and C, the apex chosen for measurement is the point of angulation. This usually corresponds to the highest point of the artery. Since the landmarks chosen are all essentially mid-line structures, slight degrees of obliquity do not disturb the ratio markedly.

loop. Moreover, the recognition of "the apex of the cranial loop" is not always straightforward. In general, the highest point of the loop was taken as the apical point when the roentgenogram was oriented so that Twining's line was horizontal. In those cases with acute angulation of the

anterior limb on the connecting segment of the cranial loop, the apex chosen was the point of the angulation. In most instances, this also corresponded to the highest point of the cranial loop.

The description and the examples of the normal and pathologic material included in

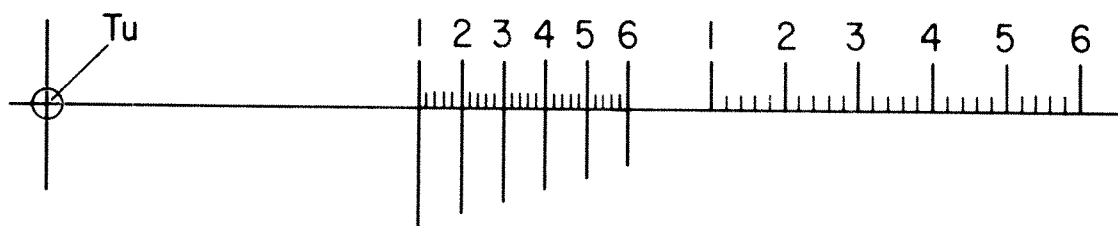


FIG. 19. A 56 per cent proportional or double scale. Actual size. In use, this is drawn on transparent film and superimposed on the lateral angiogram. The origin (o) is placed on the tuberculum sellae and Twining's line oriented to run through the point posteriorly selected to represent the internal occipital protuberance. One notes the division on the outer scale at the occipital point. The foot of the perpendicular from the cranial loop to Twining's line intersects the inner scale at some scale division. If this is the same division as on the outer scale, the ratio of the selected distances is 56 per cent. If it is less or greater by one, two or three divisions, the percentage is correspondingly smaller or larger. For greater deviations, actual measurements and an arithmetical calculation should be made.

this report are obviously based on selected cases. There is still a substantial number of instances in which little useful information can be obtained from visualization of the posterior inferior cerebellar artery because of its bizarre appearance. With additional experience, however, these cases should become less frequent as it becomes possible to systematize and recognize the more common normal variations and pathologic changes.

SUMMARY

1. Despite numerous variations, it is possible to select a configuration of the posterior inferior cerebellar artery in both the lateral and anteroposterior projections which can be considered as typical or standard.

2. The main segments of this vessel correspond to structures occupying the inferior portion of the posterior fossa. Conclusions as to the size and configuration of these structures can therefore be based on the appearance of this vessel.

3. Displacements and deformities of the posterior inferior cerebellar artery may be interpreted in terms of the typical configuration and are of considerable importance in the recognition and localization of expanding lesions.

4. A semi-quantitative evaluation of anteroposterior displacement of the apical portion of the cranial loop in the lateral

projection is presented which may be of assistance in questionable cases.

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THE SIGNIFICANCE OF PROTEIN BINDING OF CONTRAST MEDIA IN ROENTGEN DIAGNOSIS*

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THE radiologic literature contains numerous experimental and clinical observations that relate to the toxicity and the excretory pathways of contrast media, but there have been relatively few reports of attempts to ascertain the underlying physical-chemical phenomena that govern these excretory pathways and toxicity. From these few studies,^{1,3,4,12,31,32,37} however, it is immediately apparent that an enhancement of our cumulative knowledge in this sphere should serve as a guide for development of less toxic and more organ-specific media. Accordingly, a study of the binding between some of the contrast media used in clinical radiology and the whole serum of a number of animal species has been undertaken utilizing the method of equilibrium dialysis. Details of these binding studies will be the subject of a separate communication. The basic significant information can be summarized as follows:

1. Cholografin* and urokon* bound to serum albumin but not to a significant degree to alpha, beta, or gamma globulin.

2. Serum and plasma binding values for urokon,* cholografin,* and hypaque* were identical.

3. The binding characteristics of non-radioactive materials were determined by a method of competitive inhibition in which both the material in question and one of the labeled contrast media were placed in the same bath and dialyzed against the same protein aliquot. Under these conditions, a reduction in the established ratio of bound/

free labeled contrast media represented occupation of available binding sites by the nonlabeled material. By this method, it was shown that cholografin, urokon, hypaque, and miokon all appeared to compete for the same site on albumin. The strength of the bond was greatest between albumin and cholografin and weakest between albumin and miokon (Fig. 1). Diodrast appears to be bound to some other receptor site on albumin.

4. The binding capacity between the urokon* and the sera from 13 species was also studied and a great variation was observed (Table I); sheep, horse, and calf serum bound urokon* the best; human, rat, and pig bound urokon* intermediately well;

TABLE I
THE BINDING OF I* UROKON BY 1:5 DILUTION OF
SERUM FROM DIFFERENT SPECIES
γI* Urokon Bound/ml.

0.057 γI* Urokon Free	
Sheep	10.69
Horse	4.95
Calf	3.90
Human	1.97
Sprague-Dawley Rat	1.60
Holtzman Rat	1.47
Pig	1.30
Giraffe	0.63
C 57 Mouse	0.62
Cat	0.32
CFW Mouse	0.29
Guinea Pig	0.25
Rabbit	0.21
Dog	0.14
Chick	0.04

* The asterisk will be used to symbolize media tagged with I¹³¹. The full chemical formulae for these media are well known and readily available and will not be detailed in this report.

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THE RELATIVE CAPACITY OF EQUIMOLAR SOLUTIONS OF UNLABELED, BENZOATED COMPOUNDS TO INHIBIT THE BINDING OF I* UROKON BY ALBUMIN

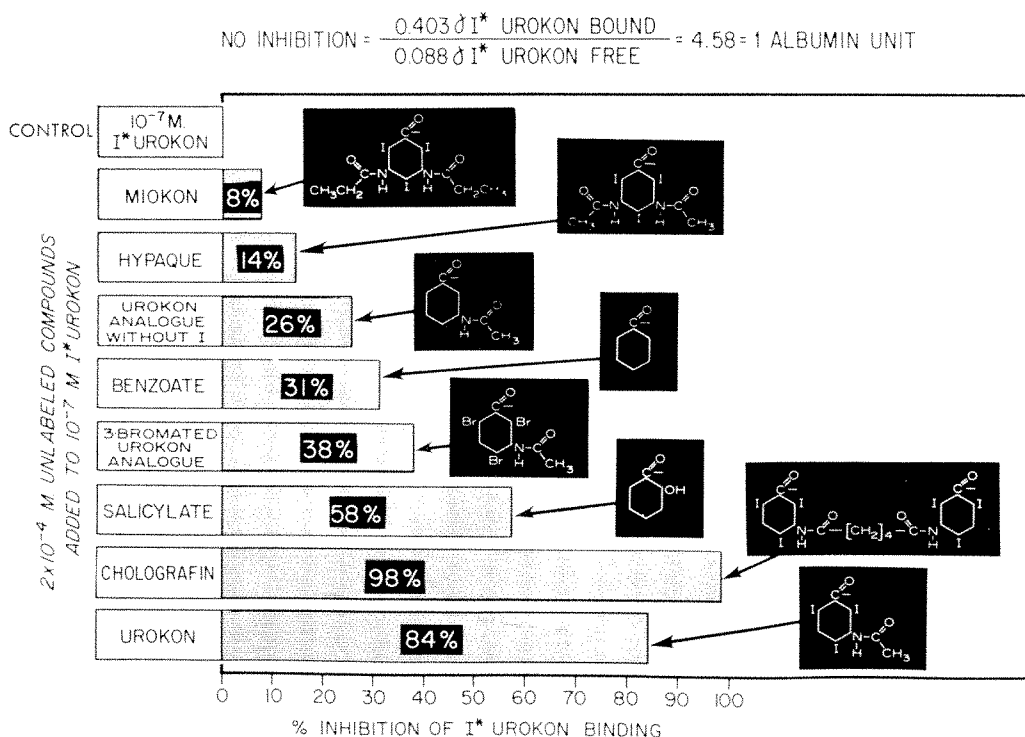


Fig. 1. The relative competitive inhibition of the albumin binding of a 10^{-7} molar solution of urokon* by a series of substituted benzoic acid derivatives. The greatest degree of inhibition is exerted by cholografin.

whereas giraffe, mouse, cat, guinea pig, rabbit, dog, and chick bound urokon* the least. Hypaque* did not bind to a significant extent with the serum of any of these species.

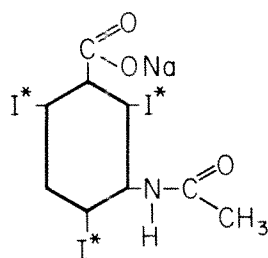
The striking variations in the binding of separate contrast media by the serum of a given species and the range in binding capacity observed for the same contrast medium by different species led to the present investigations which were undertaken in an effort to determine what role, if any, should be assigned to the protein binding capacity of contrast materials in determining excretory pathways and toxicity.

SOME PHYSICO-CHEMICAL CONSIDERATIONS

Urokon, hypaque, and cholografin have distinct but related structural frameworks

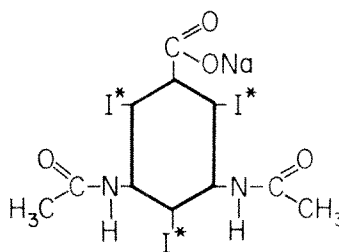
at the molecular level (Fig. 2 and 3). A consideration of these structural differences and the binding affinities of the three substances suggest that the presence or absence of an acetamino group or other prosthetic structure in the 5 position of the benzene ring is an important determinant. When this group is present as it is in hypaque and miokon, the binding potential for albumin is poor. When this position on the benzene ring is empty as in urokon and cholografin (essentially a dimolecular form of urokon), the substance binds to albumin in a relatively strong fashion. The evidence suggests, then, that the presence of an unguarded hydrogen atom in numerical sequence to an iodine atom on the benzene ring increases the binding capacity of any of these contrast materials.

UROKON



M.W. 579

HYPAQUE



M.W. 636

FIG. 2. The chemical structures of urokon and hypaque.

A similar relation of binding to structure was pointed out by Gregersen and Rawson²⁷ who found that Evans blue, a tolidine dye that bound tightly to albumin differed from trypan blue, a relatively poor albumin binder, only in the position of its sulfonic acid radicles on the naphthalene ring. A shift in the sulfonic acid radicles from the 2, 4 (Evans blue) to the 3, 6 (trypan blue) positions profoundly increased the disappearance rate of the injected material from the blood stream, presumably a reflection of a greater protein independence.

The dynamics of albumin binding have been reported for a large number of substances. Undoubtedly, albumin serves as a physiologic transport mechanism for many of these. In an excellent review of the transport of fatty acids, Fredrickson and Gordon¹⁸ point out that unesterified fatty acids bind quantitatively to albumin and that each albumin molecule bears a discrete number of binding sites to which fatty acids are bound. The interaction of any one site with a fatty acid is a simple association-dissociation equilibrium that obeys the law of mass action and can be described quantitatively by an association constant. These authors feel that "it would be extraordinarily difficult to conceive of any molecular basis for such strong interactions as those observed in the unesterified fatty acid-albumin system without invoking an electrostatic factor derived from mutual attraction of the carboxylate anion and some positively charged group on the sur-

face of the albumin molecule." Concerning the same interaction, Goodman²⁶ described a number of available binding sites on each albumin molecule for fatty acids. He described two sites with very high affinity, five with a lesser affinity, and a large number (approximately 20) with a much poorer affinity for fatty acids. Odell,⁴² who quantitated the binding capacity of albumin for bilirubin, noted that the specific molecular sites for the binding of these two substances was not known but probably involved the cationic amino groups of albumin and the carboxyl groups of the propionic acid side chain of bilirubin. He pointed out that at pH 7.9, one mol of albumin bound 3.3 mols of bilirubin, while at pH 7.4, one mol of albumin bound only 1.9 mols of bilirubin.

Many other organic anions associate with albumin, and a partial list of these includes caffeine sodium benzoate, salicylate, some of the sulfa drugs,⁴³ bromsulphalein, and other organic dyes,⁴ the barbiturates,⁶¹ etc.

Block *et al.*⁶ working with diodrast touched on the influence of anion concentration in the binding phenomenon when

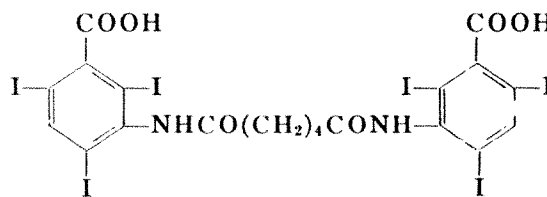


FIG. 3. The chemical structure of cholografin

they indicated that *in vitro*, some serum protein binding of diodrast* occurred at all concentrations below 1 mg. per cent but in concentrations below 1 to 2 μ g. per cent, diodrast* was bound to the extent of being practically nondialyzable.

These, then, represent some of the considerations involved in the dynamics of albumin binding. It is obvious that any experiments designed to quantitate binding to albumin must not fail to take into consideration some of the pitfalls that may present themselves. Thus, utilization of a "clean" albumin with all potential binding sites available, careful control of pH and anion concentrations are prerequisites. It is also obvious that further advances in our knowledge of binding phenomena will depend largely on further elucidation of exact albumin structural characteristics.

FACTORS THAT MAY BEAR ON LOCAL AND SYSTEMIC TOXICITY

A. THE CORRELATION BETWEEN PROTEIN BINDING AND TOXICITY

Previous appraisals of the toxicity of contrast media have, with few exceptions, been primarily concerned with LD₅₀ dosages systemically or with alterations in a specific organ's function or histology. As far as can be determined, only Knoefel and Huang³⁷ have entertained the notion that protein binding may be significant in toxicity considerations. In view of the fact

that our preliminary observations on protein binding suggested some correlation between toxicity and binding values, we decided to determine the relative binding affinities of a number of contrast media in the mouse, rat, dog, rabbit, and human. The results of this study are noted in Table II.

It is apparent that there is an order of species precedence in binding that is unique for each of the contrast materials. Thus, with cholografin, the human has a more avid albumin bond than does the dog, rat, rabbit, or mouse, in that order. For diodrast, on the other hand, the most avid albumin bond is found in the rabbit. This equals approximately that found in the rat, and these are greater than that found in the human, dog, and mouse, respectively.

When the binding data for 3 species, expressed in terms of mols bound/mols free are plotted on semi-logarithmic paper against averaged published LD₅₀ intravenous dosages expressed as millimols/kg. in the same species, a definite correlation can be noted. Except for urokon in the two rodent species, there appears to be a consistent correspondence between binding and toxicity. The better-bound materials are also the most toxic. The single exception, urokon in the rat and mouse, shows a lesser degree of toxicity for its binding than would be predicted from the remainder of the plotted values (Fig. 4).

TABLE II
THE RELATIVE BINDING CAPACITIES OF 1:5 DILUTIONS OF SERUM FROM FIVE SPECIES

Contrast Media	Molarity of Unbound Media	Bound/Unbound Ratio for Single Serum Samples from Five Species				
		Human	Dog	Rat	Rabbit	Mouse
Cholografin	$1.15 \times 10^{-7}M$	12.18	11.52	10.32	5.28	1.98
Urokon	$1.03 \times 10^{-7}M$	Human 3.58	Rat 1.46	Mouse 1.41	Dog 0.96	Rabbit 0.33
Diodrast	$1.57 \times 10^{-7}M$	Rabbit 0.17	Rat 0.17	Human 0.09	Dog 0.03	Mouse 0.02
Hypaque	$1.43 \times 10^{-7}M$	Human 0.05	Rabbit 0.03	Rat 0.02	Dog 0.01	Mouse <0.01

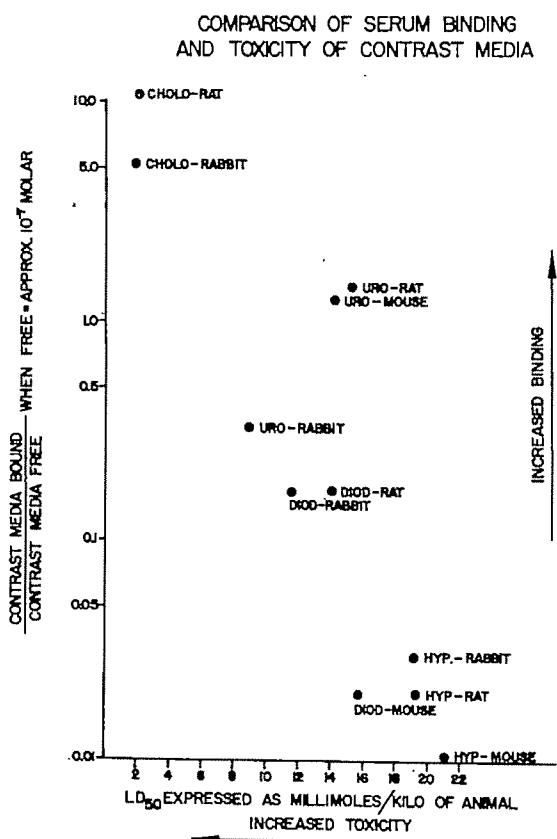


FIG. 4. The correlation between binding and published LD₅₀ toxicity figures.

B. THE CORRELATION BETWEEN TOXICITY AND ALTERATIONS IN BLOOD AND BLOOD VESSELS

The recent reports by Sobin and his co-workers,⁵⁸ Bernstein and Evans,⁵ and Read⁵² suggest that blood sludging may result from injections of some of the contrast media. The physiologic significance of red blood cell sludging has been adequately covered by Brooks and his co-workers⁸ in this country and by numerous Swedish investigators.^{10,12,14,22,59}

In a previous report from this laboratory,⁴¹ attention was drawn to a spectrum of toxicity that could be assigned to certain of the contrast materials available for common use in prepared concentrations. The same general observations that we made utilizing the dog's kidney as a test object have been made by numerous other investigators,^{17,29,35,45} touching on almost all organs and systems. Our data indicated

that contraction of the kidney, a phenomenon that must come about through contraction of the vascular elements, resulted as a transient immediate aftermath of 70 per cent diodrast injections and as a sustained aftermath of 70 per cent urokon injections into the renal arteries of dogs. Necrotic changes noted in the kidney parenchyma under these circumstances appeared to follow the vascular distribution.

There is also available now a large body of evidence that suggests that changes in vascular permeability underlie alterations in local physiology or histology noted after intravascular injection of the contrast media.^{7,17,29,32,40,45} Furthermore, there are now at least two reports of endothelial injury in the experimental animal demonstrated by special techniques after intimal applications of various contrast media.^{39,64}

In view of the data cited above, several simple experiments were designed to test the possible effects of contrast media on blood. Varying dilutions of commercially available contrast media and their analogues were incubated at room temperature with: (a) human whole blood, and (b) washed human red blood cells. Moist preparations of these contrast-blood or analogue-blood solutions were examined under the oil immersion lens of a microscope. The results of these incubations with a 1:100

TABLE III

EFFECT OF CONTRAST MATERIAL ON WHOLE BLOOD

1:100 Dilution	Crenation-Prickle cell	Agglutination	Rouleaux
70% Urokon	++++	+++	o
52% Cholografin	++++	++	o
70% Diodrast	++++	+++	o
50% Miokon	+	o	o+
76% Renografin	o	+	++++
90% Hypaque	+	o	o+
75% Unipaque*	o	o	+++
60% MI-216†	+	o	o

* Methylglucamine salt of 3,5-dipropionamido-2,4,6-triiodobenzoic acid.

† 5-acetamido-N-methyl-2,4,6-triiodoisophthalamic acid.

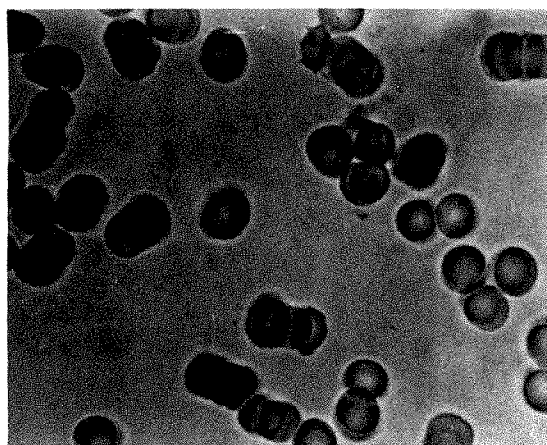


FIG. 5. Whole blood incubated with normal saline.

dilution of a number of contrast media are summarized in Table III and illustrated in Figures 5 to 9. Cholografin, urokon, and diodrast produced a change in the erythrocytes not duplicated by the other tested media. This change was not related to osmolarity and did not correlate with known viscosity or pH differences. It was associated with agglutination as distinct from rouleau formation. It should be noted that the contrast media that produced the major changes in red blood cell morphology were also the contrast media that showed relatively good binding as previously detailed. Diodrast is actually not in the same binding class as urokon on a molar basis, but it is a better binder than hypaque, and

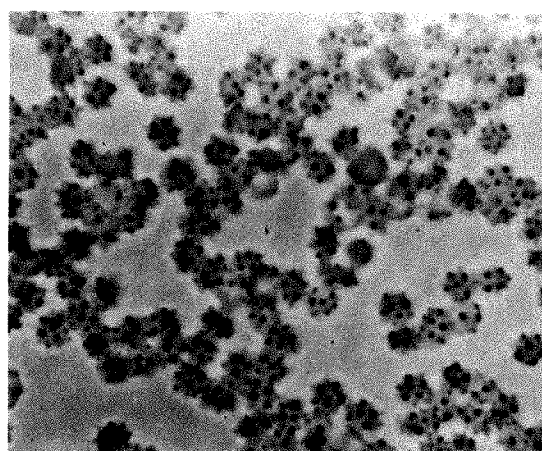


FIG. 7. Whole blood incubated with 52 per cent cholografin (1:100 dilution).

had greater relative molarity in the test solutions. Incubation of contrast media with washed red blood cells proved somewhat unsatisfactory because of technical artifacts. It was evident, however, that rouleau formation was not produced with the washed cells. Maximal crenation did occur in the same mixtures as noted in the whole blood preparations, but occurred also to some degree with almost all the mixtures. Furchgott and Ponder^{19,20,49} have described what they term a "disc-sphere transformation" in mammalian red blood cells. Beginning with an interesting series of observations on the effects of cover glass and slides on the morphology of the red

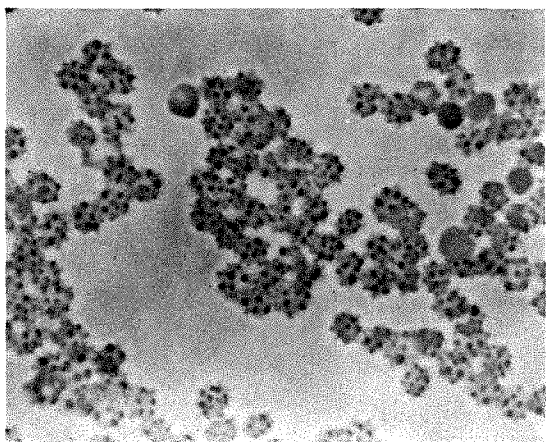


FIG. 6. Whole blood incubated with 70 per cent urokon (1:100 dilution).

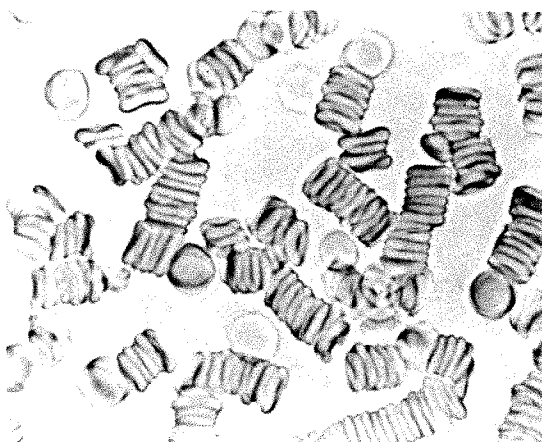


FIG. 8. Whole blood incubated with 76 per cent renografin (1:100 dilution).

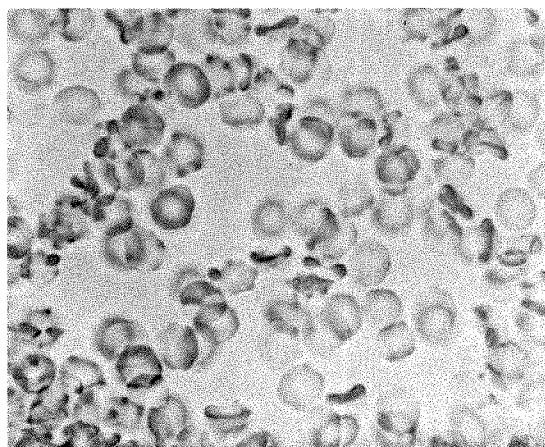


Fig. 9. Three times washed red blood cells incubated with 76 per cent renografin (1:100 dilution).

blood cell, they deduced and then confirmed the fact that major changes in pH or more modest changes associated with adsorption onto glass of an "anti-sphering" substance from the red blood cell surfaces caused the cells to undergo a sequential series of changes beginning with the usual disc and changing in order to a crenated disc, a coarsely crenated sphere, a finely crenated sphere, and finally, a perfect sphere. Beyond this stage, hemolysis took place. They deduced from their investigations that the anti-sphering substance which protected against this transformation was crystallin and represented an important component of the erythrocyte surface ultrastructure.

We attempted to determine, if possible, the role that albumin might play by virtue of its position in or around red blood cells by utilizing I^{131} -tagged human serum albumin mixed with appropriate concentrations of 25 per cent human serum albumin in serial dilutions and incubated at room temperature for four hours with washed human red blood cells filtered through glass beads. Following this incubation, the erythrocytes were centrifuged and hematocrits obtained. By appropriate calculations of the count before and after the centrifuge, we were able to determine that a small amount of tagged albumin (approximately 5 to 7 per cent) appeared to come down

with the red blood cells. It was impossible to determine with certainty whether this might be situated in a colloidal aggregation about the red blood cells or within the ultrastructure of these cells. When a similar study was repeated with varying dilutions of urokon* incubated together with washed human erythrocytes, a small amount of urokon also appeared to come down with the cells (approximately 4 per cent).

It is evident from the data cited above that in these *in vitro* experiments, small amounts of urokon, possibly bound to albumin in or around the red blood cells, produced a change in the appearance of these cells. The same change was found with cholografin and, to a somewhat lesser degree, with diodrast. Freezing point depression values were obtained on all the diluted materials incubated together with blood for the morphologic observations. These indicated that osmolarity differences did not account for the changes in the erythrocyte shape and crenation. The bromine-substituted and the noniodinated analogues of urokon produced 3+ crenation but no agglutination. Bromine-substituted hypaque and noniodinated hypaque reacted like hypaque itself. We were also able to show in these morphologic observations that rheomacrodex (low molecular weight dextran) did exert some stabilizing effect on blood incubated with urokon, and that the substance with the highest percentage of methylglucamine in the mixture (76 per cent renografin) produced a maximal rouleau formation. This was not visibly affected by additions of rheomacrodex. Rheomacrodex appeared to exert a greater protective effect on the whole blood-urokon mixtures than on the washed cell-urokon mixtures, suggesting the possibility that its stabilizing action was mediated through a serum component.

C. ALBUMIN: ITS HYPOTHETICAL ROLE IN TOXICITY

The relation of the blood elements and blood vessels to contrast toxicity is suggested by the data cited from this labora-

tory and from a pertinent review of the literature.

From the standpoint of systemic toxicity, death in the experimental animal has been ably summarized by Hoppe³² who concludes that the symptoms observed at death in the experimental animal injected with large amounts of contrast media can be divided into two major categories, convulsions and capillary breakdown in the lungs. In the clinical field, the historical and statistical review of deaths occurring in excretory urography by Pendergrass and his associates⁴⁸ points up the frequency with which myocardial infarction has turned up as the cause of death in a series of 156 intravenous urography fatalities collected from all over the country. From the direct standpoint, anyone who has had personal experience with peripheral arteriography can attest to the immediate pain often evoked in patients on injection of the contrast bolus into the vessel. As in most of the studies cited above, this was far more impressive with the media utilized prior to the advent of the (relatively) poor protein binders.

Having maintained that there is a positive correlation between protein binding and toxicity and that toxicity usually involves physiologic or anatomic alterations in the vascular elements or vascular walls, one has yet to explain the bond that might connect protein binding with the blood elements and the blood vessels (Fig. 10).

The linkage that closes the triangle here may take the form of albumin and depends on two assumptions: (1) albumin is present in association with red blood cells and vascular endothelium and is necessary, in part, to maintain structural or functional characteristics; (2) a contrast substance bound to albumin in sufficient quantity may in some fashion alter its capacity to maintain the physiologic and/or structural integrity of the tissue with which it is normally associated.

The protein anti-sphering substance in red blood cells mentioned by Furchgott and Ponder^{19,20} has already been touched

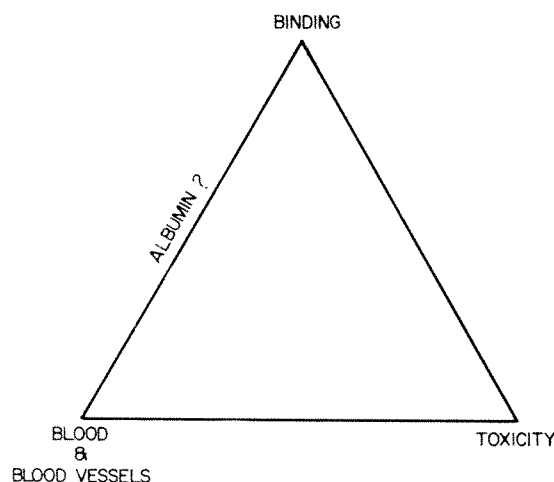


FIG. 10. The interrelationships of protein binding, toxicity, and the vascular elements.

upon. It is impossible to say with assurance from their work or from our own whether albumin is actually within the cell or is in the colloidal aggregation about the cell. Thorsén and Hint⁵⁹ point out that blood cells, rouleau formations, and cell masses are covered by a thin surface coat derived from the plasma. Under favorable circumstances when rouleaux are drawn out or deformed or masses are separated one from another, this coat is stretched out to form clearly visible threads. This formation of film in colloid solutions at phase boundaries comparable with the borderline between blood cell surface and plasma is a well-known phenomenon. It is this surface film, according to Thorsén and Hint, that leads to rouleaux, since surface tension considerations cause the film-covered red blood cells to lay their flat surfaces one against the other in order to present the smallest total surface to the surrounding fluid. The film or gel phase surrounding each cell contains colloids which are in equilibrium with colloids of the plasma. The addition of low molecular colloid to the plasma (for example, low molecular weight dextran) reduces the average molecular weight of the entire system and, if reduced below a critical level, causes a dissolution of the surface film and therefore a break-up of any aggregation that had formed. It does not

appear clear at the present time, however, exactly how dextran exerts its protective influence in the animals injected by Bernstein and Evans⁵ with 90 per cent hy-paque. This may be better understood when these experiments are repeated with some of the other contrast media and when the role in sludging that should be assigned to crenation-agglutination as opposed to rouleaux-agglutination is better elucidated.

In addition to whatever role albumin may play in blood sludging, it is worthwhile noting that blood vessels stained with a fluorescein-tagged anti-albumin show good staining for albumin in the endothelial layer with traces of albumin presenting beyond the basement membrane as well (Fig. 11). The presence of albumin in blood vessels in many areas of the body has been adequately documented by Gitlin and his co-workers.²³ The availability of an endothelial binding site for opaque material is thus apparent.

Regarding the second assumption, there is no direct evidence that binding a contrast substance to albumin in sufficient

quantity may somehow alter its physiologic capacity to maintain functional integrity. Fredrickson and Gordon,¹⁸ however, have indicated that palmitate, an albumin binder in human blood, would be bound to blood cells to the extent of about 1 per cent. Furchgott and Ponder^{19,20,49} had shown that traces of oleic or palmitic acids caused the cells to undergo a crenation sequence and to act as if deprived of their anti-sphering substance. We have further indirect evidence of the effects of contrast materials on structural integrity in that these media, when passed through the lumen of a blood vessel, have been noted to exert their major morphologic changes at their sites of maximal concentration.^{7,39} It should be stated parenthetically that changes in permeability need not be accompanied by obvious changes in morphology assessable by our present techniques. The binding of some substance to albumin might, for example, result in a change in the over-all charge or in molecular shape without any visible morphologic alteration.

FACTORS THAT MAY BEAR ON EXCRETORY PATHWAYS

A. ATTEMPTS TO ALTER SERUM BINDING BY COMPETITIVE INHIBITION

Bang and Georg³ noted that the introduction of a chlorine, bromine, or iodine atom into the phenolphthalein radicle seemed to lead to combination with the plasma proteins and almost selective excretion in the bile. Bennhold and his co-workers⁴ in 1950 correlated the protein binding capacity of a number of organic dyes and several contrast media with what they considered to be their "hepatotropic and nephrotropic" properties. They emphasize that a number of their "nephrotropic substances" are in fact bound to albumin but on the basis of a very labile equilibrium dissociation constant rather than on the basis of a firmer binding. In the course of the present study, it soon became obvious that the more highly bound materials were those that were commonly used



FIG. 11. Section of an infant aorta stained with an anti-albumin antibody labeled with fluorescein. The fluorescein tag cannot be adequately identified in this black and white print. It lies principally in the area of the white autofluorescent basement membrane.

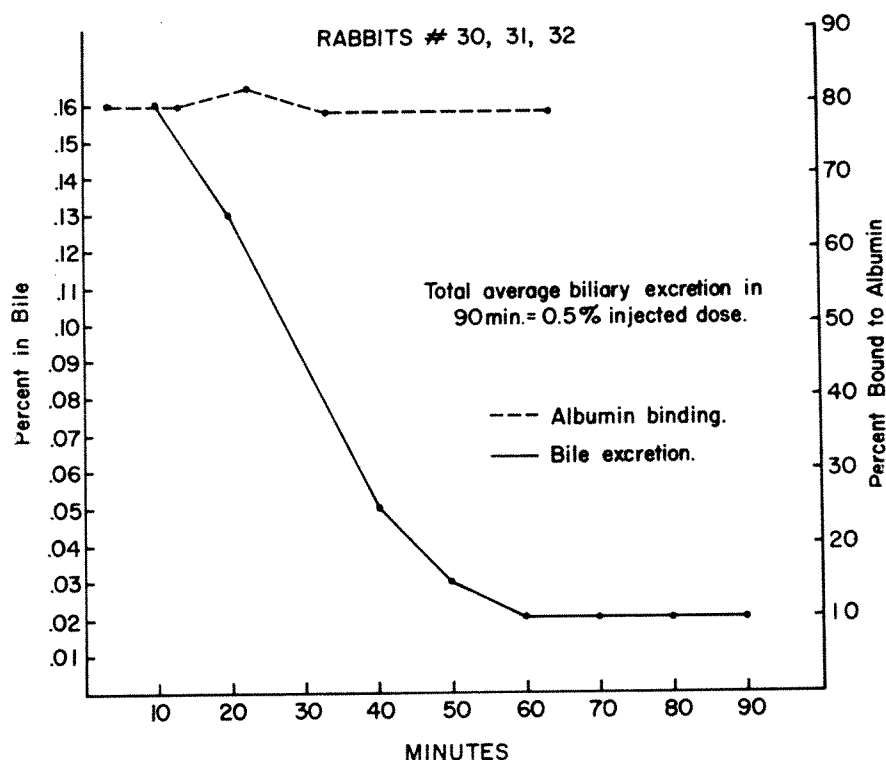


FIG. 17. Average binding and biliary excretion values for 3 rabbits primed with *human* serum albumin (I.V. 30 cc./kg. of 6.2 per cent HSA) and then injected with a mixture of urokon*+urokon (200 mg./kg.).

binding values, but without a concurrent increase in biliary excretion. Failure to increase biliary excretion in this circumstance was at first disturbing, but might be explained by the realization that induced metabolic alkalosis and acidosis are reflected immediately in the plasma, in one to two hours in the extravascular extracellular fluids, and only in four to five hours or more in the extravascular intracellular fluids.⁵³ This latter area, as a matter of fact, may show an opposite change in pH consequent to ventilatory factors, and the rapid diffusion of CO₂ gas in all body compartments. A diminution in serum binding capacity by induced metabolic alkalosis will interrupt the contrast transport sequence at the plasma level and diminish the amount available to the liver cell regardless of the intracellular pH. On the other hand, increasing the serum binding capacity by induced metabolic acidosis may increase the absolute amount of bond

material offered to the liver cell, but provides no mechanism for increased uptake by the cell. As will be noted subsequently, an unfavorable increase in the pH gradient between the extravascular and intracellular areas may actually be promoted in this fashion, leading to an interruption of the excretory transport mechanism at the entering cellular level.

Finally, it must be recognized that the alkalosis and acidosis induced in these experiments may lead to sufficient general deterioration of the animal to alter excretory pathways in an unpredictable fashion.

DISCUSSION OF FACTORS THAT MAY BEAR ON EXCRETORY PATHWAYS

In the practice of clinical radiography, the occurrence of a "heterotrophic" excretion of a contrast material is found often enough to merit notice. This almost always takes the form of an inversion of the expected renal-liver partition for any given

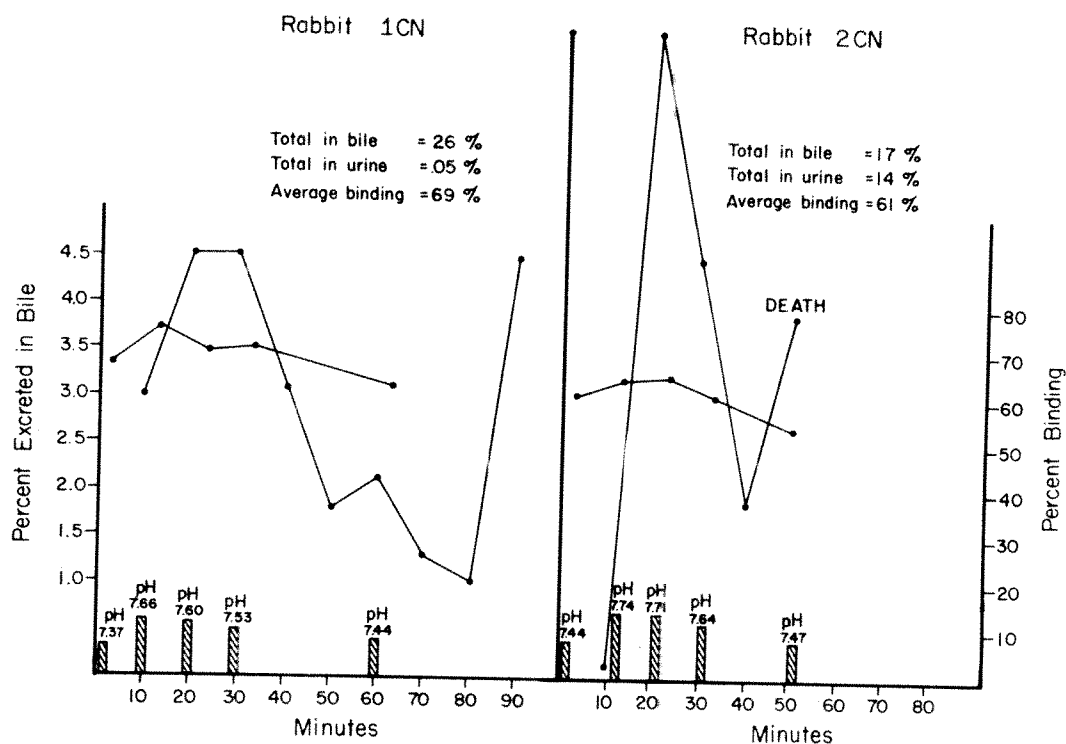


FIG. 18. The biliary excretory values and the serum binding values for 2 rabbits with induced metabolic alkalosis and injected with a mixture of cholografin*+cholografin (100 mg./kg.).

material. From our own experience this has happened most often with cholografin and with urokon, in the absence of obvious liver or renal disease. This phenomenon of occasional "heterotrophic" excretion has been noted by others as well; Orloff⁴⁶ commenting on the employment of urokon for cholecystography and Arendt and Zgoda² commenting on the occasional gallbladder shadow noted after administration of hypaque. It seems likely that most, if not all, available contrast media are capable of being excreted in both the bile and urine, although in some species, the absolute amount excreted in one area or the other may be quite insignificant and difficult to detect.

From a practical standpoint, it is important that an attempt be made to determine why a particular contrast material is preferentially excreted in either the liver or bile in order to formulate a more rational approach to the construction and consideration of new media. Epstein *et al.*¹² consider-

ing the question of the relation of chemical structure to function for cholecystographic material suggested that some of the requirements for a good oral cholecystographic agent include: (1) a molecular structure which enables the substance to be borne to the liver (should include a phenolic group, known to be detoxified in the liver as the glucuronide or sulfate ester); (2) a carboxyl group in the molecule so that the sodium salt may be formed to facilitate the solution of the compounds in bile; and (3) fat solubility, so that the substance will pass through the liver and gallbladder rather than through the kidney.

Archer,¹ studying a group of compounds analogous to those of Epstein *et al.*¹² found, as did Epstein, that the length of the side-chain on the iodinated aromatic ring is of extreme importance in directing a compound into the bile. In the case of the triiodinated compounds, Archer found that optimal lipophilic activity was associated with side-chains of intermediate size (in

addition to a "bridging group" and a carboxyl group). When the side group is too large, poor visualization results, and when too short, the compound is excreted in the urine.

Wallingford,⁶¹ on the other hand, has pointed out that for urokon maximum aqueous solubility (and LD₅₀) were obtained when there were two carbons in the acyl group (acetyl), promoting presentation in the urine.

Previous mention has been made in this paper of the relation of chemical structure of contrast media to protein binding activity. Bang and Georg³ are careful to point out in their remarks on the association of protein binding of the halogenated phenolphthaleins to selective biliary excretion that this selective excretion cannot be dismissed by merely saying that these substances fail to diffuse out the glomeruli by virtue of their protein association, since the excretion of phenolphthaleins is predominantly by the tubules. Smith⁵⁷ has noted that even substantial protein binding is quite compatible with tubular excretion as have Knoefel and Huang.³⁷ In clinical practice with the contrast materials, however, the high plasma concentrations attained implicate glomerular filtration as the predominant or significant renal excretory mechanism.^{6,38,51}

It is important to this discussion to stress that any consideration of protein binding of the contrast media implies a comparison of *relative* binding values, and in all probability, every contrast material composed in part of an iodinated organic ring will show some degree of binding.

Perhaps the most complete consideration of the relation of protein binding to excretion of the urine-oriented opaque media to date is that of Knoefel and Huang.³⁷ By virtue of their work on renal cortical slices, they suggest that the uptake of opaque media by the renal tubular cells may be a phenomenon of protein binding rather than active cellular transport.

This same line of thought is reflected by others interested in the biodynamics of

protein binding. Odell,⁴² for example, speaking of bilirubin suggests that its distribution in the body may be considered from a viewpoint that many tissues bind bilirubin. Each tissue, then, would have its own binding affinity for bilirubin expressed in terms of a dissociation constant. Fredrickson and Gordon,¹⁸ speaking of the unesterified fatty acids (good albumin binders), cite unpublished work from their laboratory indicating that the rate of speed of binding to human serum albumin is at least of the correct order of magnitude to allow for the fatty acid associations and dissociations that might be involved in the *in vivo* turnover of these substance. In regard to the removal of unsaturated fatty acids from the plasma into extravascular tissue spaces, they note that the removal is considerably faster than is the removal of the albumin molecule itself. They speculate on the presence of receptors on all cells which have the capacity to remove fatty acids by binding them with an affinity that is at least similar to that of albumin. In this system, the first step would be removal of the fatty acids from circulating albumin to vascular endothelium. In the second step, they envision the transfer from endothelium to the parenchymal cells, the transfer being perhaps mediated by extravascular albumin.

It might be stated parenthetically that there is a dynamic exchange between the protein of the extracellular extravascular compartment and the serum protein of the vascular space and that the level of the protein in the vascular space is a reflection of the extravascular component.^{24,63}

A similar thesis of transport of the contrast materials from blood to the parenchymal cells of the liver and perhaps the renal tubules had occurred to the present authors. While no direct proof is forthcoming at this time, the present study lends support to this thesis of transport by a system of competitive binders. If, as seems probable, albumin itself represents the binding substrate in each locus, one might postulate further a local variation in pH

underlying a variable association and dissociation, specific for each area, and in total, unidirectional. Further support for this concept may be found in the review by Schanker,⁵⁵ of the mechanisms of drug adsorption and distribution. In his review he cites work by Waddell and Butler indicating that the partition of phenobarbital between plasma and tissues could be altered reversibly by varying the plasma pH. When the plasma pH was lowered, the plasma drug level decreased and the tissue levels (brain, fat, liver, and muscle) increased; conversely, raising the plasma pH resulted in an increase in the plasma level and a decrease in the tissue levels. Hanzon's³⁰ description of the secretion of uranin and its uptake by the liver further supports the feasibility of a mechanism such as we have postulated for transport by a system of competitive binders. The cumulative evidence from this study in support of such a thesis can be summarized as follows:

1. The contrast materials included in this study, and inferentially all of the current available opaque media, when bound by serum, bind almost entirely to albumin at physiologic pH levels. The degree of binding, however, varies in the fashion previously noted.

2. Opaque media of the triiodo class with an empty hydrogen atom situated between the 4 and 6 iodine atoms on the benzene ring tend in general to be *relatively* better binders, and occupancy of all positions on the ring infers a *relatively* looser bond.

3. All of the available cholecystographic media on the market today have the chemical configuration that infers relatively good albumin binding. This includes cholografin, of which the excretory dynamics in the rabbit have been detailed here. All of the urographic media of the triiodo class fall into the category of relatively poor binders. The exception is urokon, whose binding characteristics for man fall between those of the urographic and those of the cholecystographic categories. Clinical experience substantiates the not too infrequent ap-

pearance of this maverick urographic material in the gallbladder area.

4. Species variations may be marked. Epstein *et al.*¹² noted a consistent failure to visualize the gallbladder with any material tested in the chick, rabbit, and frog. Others³⁶ have commented that rabbits are not the animals of choice in the evaluation of biliary contrast media. Our data indicate that for urokon* the binding is about 8.5 times as great for man as for the rabbit and almost 50 times as great in man as compared to the chick. The binding of cholografin* is at least twice as great in the human as in the rabbit. Since there appears to be a definite relation between binding ability and biliary excretion, these data may explain the failure of the rabbit and chick as test animals for these agents.

5. Elevation of serum binding values in an artificial fashion, as was done in the HSA primed group of rabbits and by the induction of metabolic acidosis, failed to promote biliary excretion. This suggests that transport to the liver cell does not alone explain the role of binding in biliary excretion. It may necessitate a concomitant increase in the binding of extravascular, extracellular albumin components and intracellular components in the parenchymal areas. In both of these experiments, conditions were such as to favor a reverse gradient or a reduction in the normal gradient at the cellular entrance level of transport.

6. Elevation of the rabbits' physiologic pH values diminished the average serum albumin binding, and correspondingly, the per cent of injected bile-directed material actually excreted into the bile. Interruption of the transport mechanism here occurred presumably at the plasma level.

A CONSIDERATION OF SOME MISCELLANEOUS PHENOMENA

Several other considerations thought to be of importance in the biodynamics of protein binding of contrast media have arisen in the course of this investigation and will be touched upon briefly.

A. KERNICTERUS

The term "kernicterus" has been applied to the central nervous system dysfunction that may sometimes be found in patients, particularly infants, with intense jaundice.^{9,33,34} In practice, it is to be found principally among infants on the basis of prematurity, sepsis, physiologic jaundice, or blood group incompatibilities. In those who fail to survive these episodes, examination of the brain may reveal a canary yellow staining of nuclear masses, the presence of intracellular pigment on frozen sections, and evidence of degeneration of nerve cells. It has been well established now that the pigment that stains the brain in kernicterus is indirect bilirubin, and most of the evidence suggests that it is the bilirubin itself which produces the cytotoxicity.⁹

The work of Odell⁴⁴ and others indicated that a number of organic anions, including salicylate and some of the sulfa drugs, could uncouple bilirubin from albumin by successfully competing for binding sites on this protein. Previous reports of kernicterus in infants treated with sulfisoxazole diethanolamine⁵⁶ and subsequent production of this entity by a similar mechanism in a strain of congenitally jaundiced rats^{33,34} confirmed these binding dynamics.

Since both urokon and cholografin appeared to establish a tighter bond with albumin than did salicylate (Fig. 1), it occurred to us that these media might also have the potential to displace bilirubin from albumin, as salicylate did. Inasmuch as this would have considerable clinical significance in jaundiced infants, we have initiated a study of the bilirubin-contrast media binding dynamics *in vitro* and *in vivo*. The results of our *in vitro* study indicate that bilirubin can be displaced from serum protein by urokon and cholografin. Indeed, there is some evidence that this may occur *in vivo*. A lowering of the average indirect serum bilirubin level in 10 patients free of biliary or liver disease was demonstrated fifteen minutes after intravenous injection of 20 cc. of 70 per cent

urokon, although the average fall was only 0.04 mg./100 cc. of serum and is therefore of dubious significance. In a single jaundiced patient with biliary duct obstruction, an injection of 20 cc. of 52 per cent cholografin was followed by a fall from pre-injection levels of indirect bilirubin amounting to 2.2 mg. per cent, 1.2 mg. per cent, and 0.6 mg. per cent in periods of thirty, sixty, and ninety minutes post injection. In view of the relative binding dynamics of bilirubin versus urokon or cholografin in man, one would expect that injection of these materials in sufficient concentration would uncouple bilirubin and produce a transient fall in indirect bilirubin levels as occurred in Johnson's rats³⁴ (the disappearance of indirect bilirubin in these circumstances is related to its passage into available excretory pathways or into extravascular compartments, including the brain in infants or young rats). We have presently initiated a study designed to test the assumption that bilirubin might be displaced in a strain of congenitally jaundiced (Gunn) rats and might therefore lead to the production of kernicterus. Preliminary study of another rat strain, however, suggests that the relative binding dynamics may not favor displacement of bilirubin in the rat. Granted that further work needs to be done on the displacement of bilirubin by contrast materials, sufficient evidence is at hand to contravene the use of a relatively good binding contrast medium in a jaundiced infant. In a retrospective inquiry into the 2 deaths that have been definitely associated with the use of contrast media in the Children's Hospital of Pittsburgh (in the noncardiac group) during the past ten years, we have found that one was associated with an injection of 70 per cent urokon into a premature infant who had undergone an exchange transfusion a month earlier for physiologic jaundice. It is impossible, however, to state with certainty in this child whether possible bilirubin displacement played any part in this fatality or whether this might be a contrast material death of some other type.

B. PROTEIN BINDING AND THE BLOOD-BRAIN BARRIER

The whole question of the blood-brain barrier, or as Dobbing¹¹ prefers to label it, the "blood-brain-barrier system," might be once again re-examined in relation to the utilization of contrast media. Nonprotein bound organic compounds are apparently regulated in their penetration across endothelial and cell membranes of the central nervous system according to their lipid solubility and their degree of ionization.⁵⁵ The highly lipid soluble substances and the less dissociated ionic molecules tend to penetrate better into the cerebrospinal fluid and by inference into the central nervous system. On the other hand, protein-bound materials do not cross the intact endothelial membrane in this area. Tschirgi,⁶⁰ for example, has noted that trypan blue, commonly used to demonstrate violations of the blood-brain barrier, is a relatively good protein binder (relatively poor compared to Evans blue, but relatively good compared to the contrast media). In normal rats it leaves the brain unstained on intravenous application, but diffuses out into other organs, as for example, the liver. If applied *without* plasma proteins to the surface of the brain, it stains this structure to a depth proportional to the duration of the contact. If applied to the surface of the brain *with* plasma proteins, it stains the surrounding dura and muscles but leaves the brain colorless. It also stains the cerebral blood vessel on intravenous introduction down to the level of the piagial membrane.

Considering the fact that albumin occurs in the intima of vessels and realizing the now widely-held concept gleaned largely from studies with the electron microscope that there is an absence of interstitial (albumin) space in the brain,²¹ a mechanism becomes apparent that might explain many of the phenomena associated with the blood-brain barrier; for absence of an interstitial space also spells absence of interstitial fluid and lymphatic fluid, and these are necessary elements to transport protein bound materials from the vascular com-

partment to the intracellular compartment of an organ. Regardless of what the intracellular pH in the brain might be, there is then no mechanism to transport protein bound materials to the intracellular compartment, if the vascular endothelium remains intact.

Certain observed phenomena can be explained in the relationships just elaborated:

1. The penetration of intravenous trypan blue, the most widely used blood-brain barrier indicator down to the piagial membrane in juxtaposition to the endothelium, is readily explained by recalling the presence of albumin in the vessel wall (either as a structural component or "soaked-in" from the plasma).

2. Failure of the albumin bound trypan blue to extend into brain perivascular lymphatic and extracellular spaces as in other organs is due to the absence of such albumin-laden areas in the brain.

3. In cerebral angiography most malignant gliomas present as a tangle of abnormal-appearing new vessels, *without* a homogeneous diffuse stain, while meningiomas often show, in addition to abnormal vessels, a persistent, homogeneous "blush," similar to that noted in vascular tumors occurring elsewhere in the body where there is ready access to the extravascular albumin-laden fluids (peripheral sarcomas, renal tumors, etc). The meningioma, of course, is of mesodermal origin, and as such does have extravascular extracellular space. There is, on the other hand, no alternative evidence to suggest that the vascular composition of meningiomas *per se*⁶⁴ would favor the homogeneous stain or the impaired contrast circulation documented by Greitz.²⁸

4. In similar fashion one may note, as has Gardner,²¹ that the highest uptake of radioactive iodinated human serum albumin used for localization of brain tumors occurs in metastatic carcinomas, sarcomas, and some meningiomas; these tumors arise from tissues that do not possess a barrier.

5. The intravenous LD₅₀ dose in rabbits for hypaque is somewhat greater than twice

that for urokon, yet the intracisternal toxicity in the rabbit for these two substances is almost identical.³² In the intracisternal situation, protein binding no longer modifies toxicity.

6. Urokon and diodrast, good protein binders, have been shown to be more injurious to the blood-brain barrier on carotid injection than has hypaque or renografin, poor protein binders.^{7,11} Injury to the barrier has shown a definite dependence on "application time." The good protein binders are in an advantageous position to persist in the position of the albumin in the vessel wall, and from this point of vantage, exert whatever influence is germane on the integrity of this structure.

C. UROKON BINDING AND RHEUMATOID ARTHRITIS

Finally, a word or two must be said about the unexpected relation that we have noted between urokon binding ability and patients with rheumatoid arthritis. This has been mentioned in two previous communications,^{15,16} and will only be outlined here. In brief, we have found that the sera of many patients with rheumatoid arthritis have a special affinity for urokon in dilute solution, and although this is occasionally seen to a lesser extent in other disease states, the rheumatoids as a group appear to be unique. Whether this represents some inherent alteration in the albumin molecule of such patients or a disturbance in the binding and transport of some urokon-like metabolite that we cannot yet identify, remains to be determined.

CONCLUSIONS

1. Some of the protein binding characteristics of a number of contrast media have been studied.

2. The contrast media tested bind almost entirely to albumin and, except for diodrast, appear to compete for similar binding sites on this protein.

3. Direct and competitive binding studies have established the relative affinities of the tested contrast media for albumin.

4. For the triiodobenzoic acid compounds, the presence or absence of a prosthetic group at the 5 position appears to determine the relative weakness or relative strength of binding with albumin.

5. There is a marked species variation in the degree of protein binding of each of the contrast media.

6. Some of the contrast media when incubated with whole blood or washed red blood cells produce a marked degree of red blood cell crenation. This is particularly true of the better binding materials.

7. The crenation effect in red blood cells may be related to the binding of contrast media to protein in or around the red blood cells.

8. There appears to be a high degree of correlation between the strength of binding determined by equilibrium dialysis in this investigation and published reports of intravenous LD₅₀ toxicity expressed in millimols per kilogram dosage levels.

9. Evidence from this study and from the literature suggests that local and systemic toxicity from contrast materials is mediated via derangements of the blood elements and blood vessels. This may be related to the demonstrated presence of contrast binding albumin sites in or on these structures.

10. The more highly protein bound contrast media appear to be preferentially excreted in the bile and the less highly bound media in the urine. Induced alteration of binding dynamics in the rabbit suggests that excretion of a contrast substance in the bile may be dependent on a postulated system of albumin transport.

11. An *in vitro* study of the binding dynamics of bilirubin relative to some of the contrast media suggests that both urokon and cholografin are capable of competitively displacing bilirubin from albumin in the human, and therefore are theoretically capable of producing kernicterus in the jaundiced infant. These binding dynamics, however, are somewhat different in other species.

12. The absence of an extravascular tis-

sue space and, hence, an albumin space, in the brain is in keeping with the failure of contrast media and the albumin bound substances to extend outside of normal cerebral vascular endothelium. Certain brain tumors on the other hand (meningiomas, certain metastatic carcinomas, and sarcomas) do have an interstitial space. The persistent angiographic "blush" of meningiomas and some other tumors may be explained on this basis.

13. Injuries to the blood-brain barrier system by the relatively good protein binders may be related to the presence of albumin in the vascular endothelium of the cerebral vessels.

14. Urokon has a unique *in vitro* affinity for the serum of patients with rheumatoid arthritis.

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A MODIFIED LUMBAR PUNCTURE NEEDLE FOR PNEUMOENCEPHALOGRAPHY*

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ONE of the reasons for unsatisfactory lumbar pneumoencephalograms is the presence of subdural air. This causes conflicting shadows over the brain which interfere with the diagnostic qualities of the examination.

Air may enter the subdural space if the needle bevel is situated partly subdurally and partly in the subarachnoid space. Thus, the cerebrospinal fluid may flow readily, but when air is injected it passes into the subarachnoid and the subdural spaces. A traumatic puncture, or one done a day or two previously, may cause a rent in the arachnoid permitting the fluid to seep into the subdural space, thereby increasing its depth. If the needle tip rests in this area, the flow of fluid usually is diminished and the tap should be considered unsatisfactory. However, if the return of fluid is deemed adequate and air is injected, most of it may accumulate subdurally.

It occurred to us that if the lumbar puncture was atraumatic, and if the lumen in the needle tip were smaller, the incidence of subdural air injections might be lowered. A short-bevelled needle was first used, but the taps were considered traumatic because the needle tip did not permit easy perforation of the tissues.

For the past year we have been using a 17 gauge 4 inch lumbar puncture needle* with its tip modified by introducing a short soldered plug in the bevel. The bevel is 3 mm. long, about the same as that of the usual lumbar puncture needle. A 0.040 hole is bored on either side of the shaft, 5 mm. back from its extreme tip in line with the perpendicular formed by the bevel tip. The

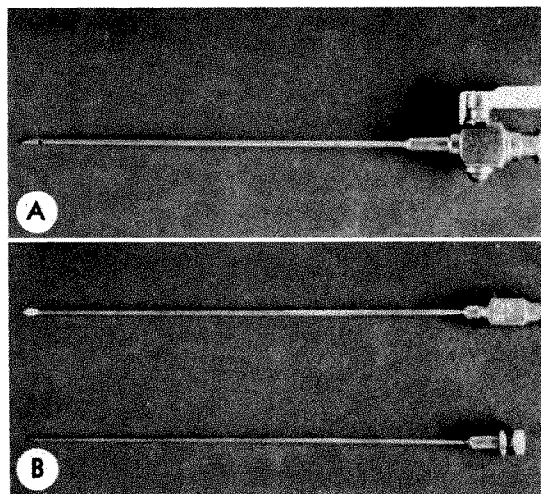


FIG. 1. (A) Modified lumbar puncture needle with stop-cock incorporated into hub. (B) Same type of needles with conventional hub and stylet withdrawn.

needle is inserted with the bevel parallel to the long axis of the canal, so that the fibers of the dura are less likely to be cut. The area through which fluid can flow is limited to these two small holes as compared with the 3 mm. length of the usual open bevel. It was felt that air was not as likely to be injected into any area other than the subarachnoid space if the holes permitted free flow of cerebrospinal fluid.

The needle is advanced with the stylet out after the skin has been pierced. Its entrance into the subarachnoid space can be identified immediately when fluid flows freely, thereby diminishing the chance of thrusting the needle point through the anterior aspect of the dura. In order to avoid possible contamination by reinsertion of a stylet, a stopcock is placed in the needle hub as soon as fluid is obtained. Recently, we have been using a needle in

* The needles were provided to us through the courtesy of Becton, Dickinson & Co., Rutherford, New Jersey.

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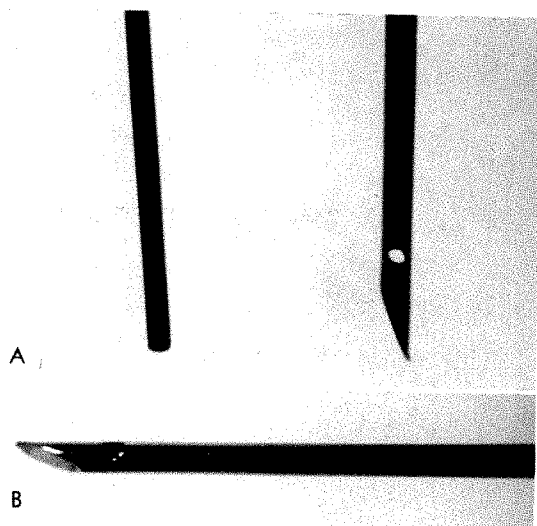


FIG. 2. (A and B) Magnified views of needle tip.

which the stopcock has been incorporated as part of the hub. This permits a somewhat better control of fluid withdrawal and air injection.

A review of the last 50 lumbar pneumoencephalograms in adults revealed 2 on which small quantities of subtentorial gas was visualized, in neither instance interfering with the diagnostic quality of the roentgenogram. One patient had fainted suddenly and had to be placed in a horizontal position with the needle *in situ*. It was felt that a small rent might have been produced, permitting a small amount of air to enter the subdural space.

A similar needle of two inch length and 20 gauge caliber is being utilized for infants. The needles for adults are also supplied to us in 18 and 20 gauge calibers.

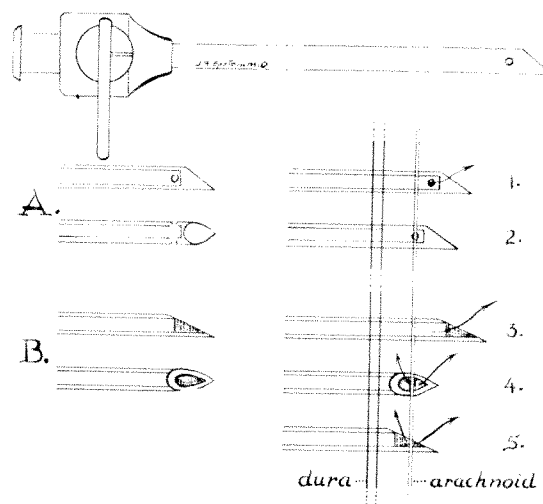


FIG. 3. A. Modified lumbar puncture needle tip: 1. Opening in subarachnoid space; 2. opening at arachnoid. B. Conventional needle tip with open bevel: 3. Bevel entirely within subarachnoid space; 4. bevel half in subarachnoid space and half in subdural space, *en face* view; 5. same positioning as 4, lateral view. The arrows indicate the flow of air.

SUMMARY

A modified lumbar puncture needle with its tip blocked and access to the subarachnoid space by way of two small holes in the shaft just above the plugged tip, has been used for pneumoencephalography in adults with a resultant low incidence of passage of air into the subdural space.

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THREE SIMPLE DEVICES TO FACILITATE CONTRAST NEUROROENTGENOGRAPHY*

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DURING the course of ventriculography it is often important to visualize the posterior ventricular system. This may require the introduction of additional air by way of the lumbar route, or the manipulation (somersaulting) of the patient by several people to effect the necessary displacement of the available air. Both methods leave much to be desired. The former requires the performance of an additional procedure with its concomitant hazards in a patient who may not be co-operative. The latter requires the assistance of several aides in addition to the personnel usually at hand. The fluid nature of the contrast medium also calls for speed in the manipulation of the patient to obtain favorable studies.

1. POSTURAL HARNESS (PARACHUTE)

Attempts to solve the above problem led to the development of the device to be described. This has proved to be most useful not only for ventriculography but also for air encaphalography, and in the general handling of the patient about the neuro-radiology unit.

The equipment consists of a standard United States Air Force parachute harness (Type III),³ a suspension unit, a chain hoist, and a track from which the unit is hung (Fig. 1). The degree of mobility of the unit is dependent upon the latitudes of motion provided by the overhead track. The chain hoist utilized is the 250 lb. Midget hoist which is fairly compact, has a desirable mechanical advantage, and an adequate safety factor. The hoist will rotate about its long axis, contributing this latitude of freedom of motion for the entire device. The chain hoist is attached to the suspension unit which causes a "trapeze" effect below.

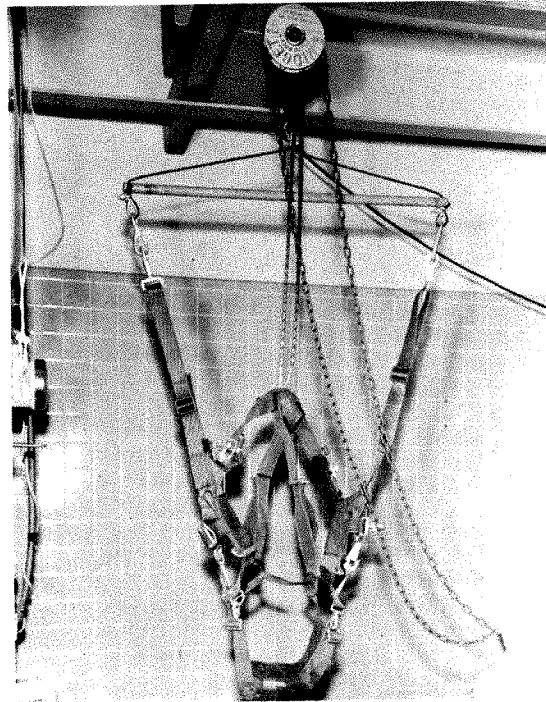


FIG. 1. The postural harness (parachute).

The suspension unit consists of a spreader bar, which is 38 inches long, with holes recessed 1 inch from either end going through the 1 inch diameter steel bar (or pipe). Steel cable, $\frac{1}{4}$ inch in diameter, is threaded through the holes at both ends of the bar. Loops are fashioned at the ends and centrally. Heavy, adjustable length web straps are attached to the cable loops and to the harness. Swivel clips are utilized at the attachment to the harness. They provide rotation along their long axis, thereby allowing the harness to be rotated about a horizontal axis. The harness is adjustable to the habitus of most adults. Suitable sites for suspension are located at shoulder and hip level (points of attach-

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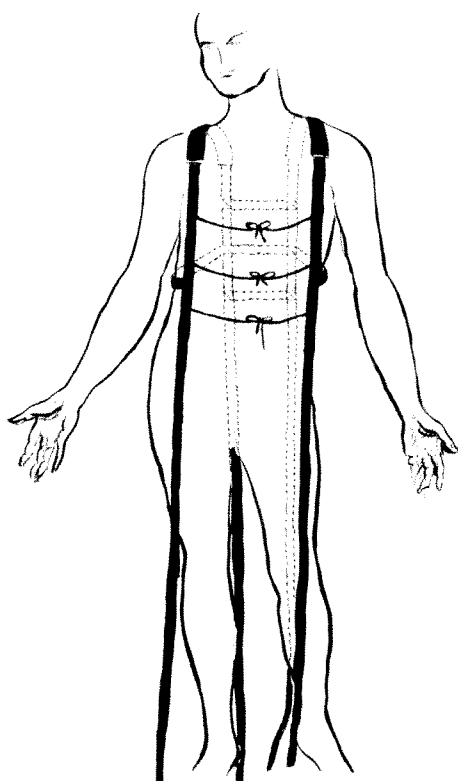


FIG. 2. Myelography harness.

ment to the harness of the risers and survival kit).

In using the apparatus, the harness may be fitted to the patient before the procedure. Caution must be exercised in fitting the leg straps about the groin. Perineal structures should be free between the straps. Padding the points of contact between the clavicles and the harness may enhance the patient's comfort. The harness need not fit as tightly as is necessary when used for escape from an aircraft.

Suspension of the harness at hip level permits for somersaulting the patient, allowing the air to flow through the third ventricle and aqueduct into the fourth ventricle. It should be remembered that in the inverted position the venous pressure to the head is increased.

Attachment of the device at both shoulder and hip levels has been useful in maintaining the upright position of patients during the various phases of air encephalography.

There is adequate access to the lumbar region in the properly fitted harness to permit lumbar puncture with ease.

The apparatus has been used to lift incapacitated patients to and from the stretcher and about the room. Two persons can carry out manipulations previously requiring four or more, with greater speed and less confusion.

2. MYELOGRAPHY HARNESS

Experienced radiologists are aware of the frustration encountered during cervical myelography, where the immobilizing device used to support the patient in the inclined plane is directly in the path of the lateral roentgen ray beam. To obtain a lateral roentgenogram of this region using a horizontal beam, the immobilizing device, which is usually manufactured of radiopaque material, must be removed. Thus the patient no longer has the benefit intended. Either the table must be returned to horizontal, thereby changing the position of the contrast medium, or some other arrangement for immobilizing the patient must be employed. This problem is very easily and conveniently overcome by the use of the harness described below. This harness was designed and used at the National Hospital for Nervous Diseases, Queen Square, London, and can be manufactured inexpensively with many advantages over the conventional more expensive equipment.

The myelography harness (Fig. 2) is constructed essentially of two 20 foot long canvas straps. The middle third of each strap which comes in contact with shoulders and trunk is padded for the patient's comfort. The "proximal" third of the padded portions are joined together by four 1 inch wide canvas strips in a fashion similar to that of railway ties, with the separation of the inner edges of the padded portions limited to 6 inches. Canvas strips are attached to the "distal" third of the padded portions for use as ties. Ties joining the lateral aspects of the straps are at the appropriate level. Most adults cannot slip

through the bounds of a harness so constructed. The four long ends of the straps are attached to the end of the myelographic table.

This harness is comfortable and patients are able to tolerate prolonged periods in the head down position. The shoulders are drawn caudad allowing a further few inches of cervical spine free for roentgenography without the superimposing shadows of the shoulders. By simply freeing the ends of the straps, the patient may be turned to the prone or supine position. This harness is very useful for supporting patients during gas myelography.

3. HEAD HALTER

The head halter (Fig. 3) consists of heavy muslin straps, 3 inches wide, which are used to support the head under the chin and around the forehead and occiput. There are three suspending straps which are used for altering the position of the head and moving it when needed.

The muslin straps are fashioned as follows: a 4 foot length passes under the chin where it is padded at its center part; the free lines pass up along the temples and are sewn to another band of muslin used to encircle the head from occiput to forehead. The closed portion of the latter strap fits around the occiput as the free ends extend forward to be wrapped about the circumference of the head and tied securely. A third strap, 18 inches long, is sewn to the midpoint of this horizontal band at the occiput. Thus, the two lines coming up from the chin along the temples and this single line coming up from the occiput are stretched above the head and used for suspension or movement. To secure the circumferential band two tapes are attached at the point at the occiput; these tie with tapes applied to the outer margins of the chin strap and make the harness secure when it is applied.



FIG. 3. Head halter.

SUMMARY

Three simple devices which have proved useful in ventriculography and air encephalography are described. The cost of construction is minimal and the advantages over conventional equipment are many.

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AN AUTOTOMOGRAPHIC APPLIANCE*

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THE value of autotomographic techniques in neuroradiology is now fairly well established^{1,2} but their routine use in pneumography is obstructed by the difficulty in performing them successfully. Even in the most experienced hands and with the most cooperative patient, autotomography can be a failure. For this reason the technique has been branded as unreliable in several centers and has been abandoned in favor of more conventional and time tested methods such as stereoscopy or routine tomography. This is unfortunate since this method is one of the simplest and most effective yet devised for visualizing midline structures, both within the brain and at the base of the skull.

The device described below has enabled us to be confident of producing successful autotomograms even under the most adverse conditions, and its use is presented in

the hope that autotomography will be more widely accepted as a basic technique.

Since the skull and atlas rotate through a central axis upon the odontoid process, it is possible to secure a tomographic cut of the midline structures within the head by having the patient merely shake his head gently, as if signifying "No." This to-and-fro movement blurs all structures lying off center (particularly the petrous temporal bones) while the midline structures, being stationary, show up in relief. When the method is successful, visualization of the third ventricle, the aqueduct of Sylvius and the fourth ventricle is dramatic (Fig. 1, *A* and *B*). Success is not invariable, however, since any deviation from the central axis through the odontoid process—either forwards and backwards, as in nodding, or from side to side—will blur the crisp image of the midline structures. Even under op-

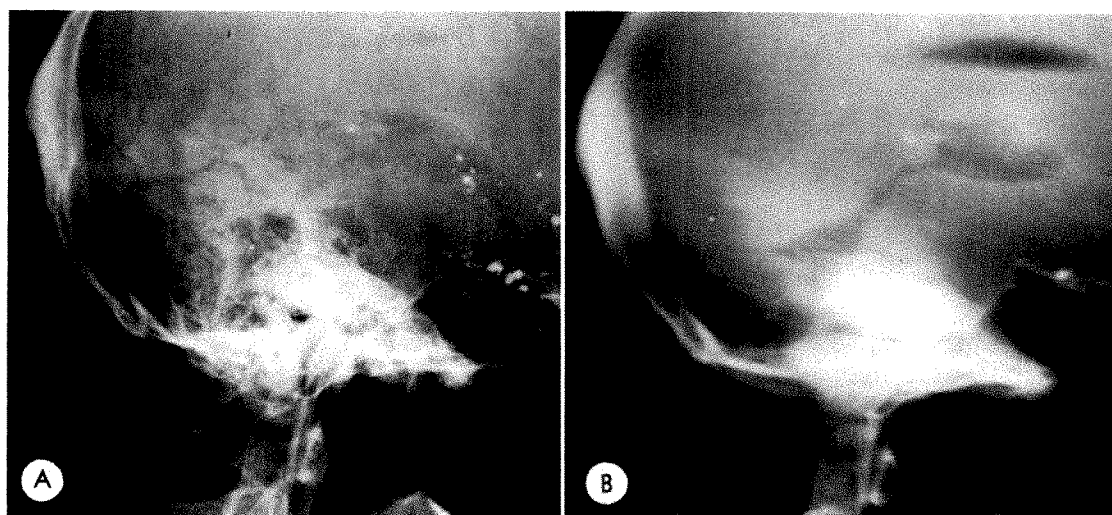


FIG. 1. (*A*) Roentgenogram taken after the injection of 8 cc. of gas. The fourth ventricle is obscured by the mastoid air cells. (Droplets of pantopaque remain in the basal cisterns from a previous myelogram.) (*B*) Autotomographic visualization of the fourth ventricle, aqueduct of Sylvius and posterior part of the third ventricle after the injection of an additional 4 cc. of gas. Note the increase in definition of the midline structures, both within the brain and at the base of the skull.

* From the Department of Diagnostic Radiology, Strong Memorial Hospital, Rochester, New York.

timal conditions it is difficult to prevent these undesired movements—a fact that can be verified by attempting the autotomographic maneuver oneself.

Ideally, for the head to move around a central axis, it should be fixed at a point on the vertex corresponding to the atlanto-axial articulation. In this way it may be rotated like a wheel on an axle, rather than its normal action like a sphere balanced upon a universal joint. While a cooperative and fully conscious patient may be able to rotate his head in one plane only, a successful autotomogram usually requires the help of an assistant's gloved hand placed upon the patient's vertex to provide a fulcrum for rotation and to guide the head through the desired arc. This involves exposure to the direct roentgen-ray beam, which is undesirable in any routine procedure.

APPARATUS

The apparatus described is intended as a detachable fitting to the Lysholm-type

skull unit, although it could be used with any conventional table. Its most important component is the rotatable circular headpiece, molded to fit the patient's head and anchored firmly upon its freely revolving axle to the skull table by a clamp. A width of canvas lined by sorbo-rubber is secured to the molded headpiece for gripping the patient's head, and this is pulled taut by an elastic band along the free margin (Fig. 2*A*; and 3*A*).

The head should be snugly but not uncomfortably held so that a cooperative patient will be able to perform the maneuver unaided. If the patient is unable to cooperate, the assistant may rotate the head by turning the handle of the axle with his gloved hand while the exposure is made. By using a diaphragm and cone, his gloved hand is well beyond the range of the direct beam. When the patient is erect, reins may be attached to the canvas head-piece over the ears, so that the assistant can retreat still further and manipulate the patient's head by remote control from behind.

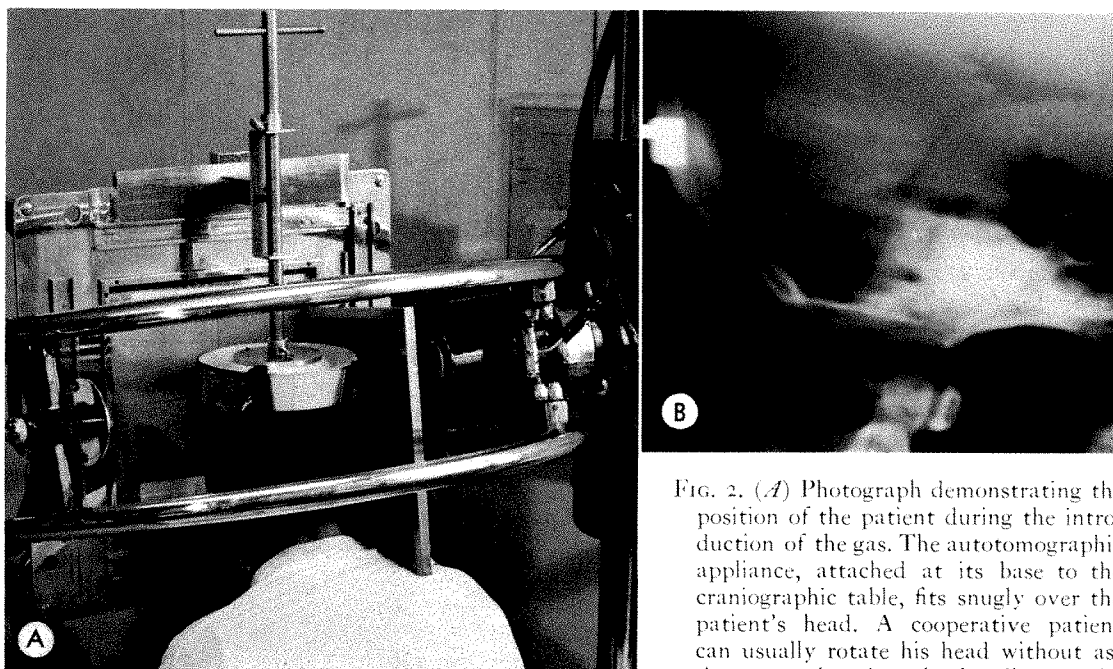


FIG. 2. (*A*) Photograph demonstrating the position of the patient during the introduction of the gas. The autotomographic appliance, attached at its base to the craniographic table, fits snugly over the patient's head. A cooperative patient can usually rotate his head without assistance; otherwise, the handle may be

turned as in Figure 3*A*. (*B*) Autotomogram of the midline structures, with gas outlining the fourth ventricle, the aqueduct of Sylvius and the posterior end of the third ventricle, as well as the ventral cisterns. The clivus and craniovertebral angle are well demonstrated.

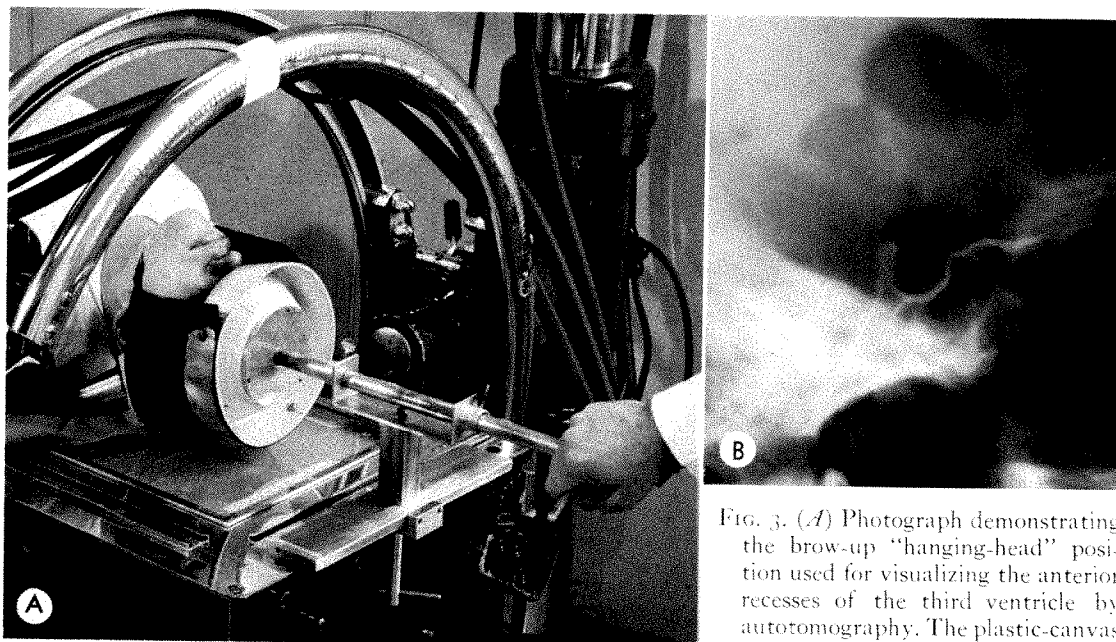


FIG. 3. (A) Photograph demonstrating the brow-up "hanging-head" position used for visualizing the anterior recesses of the third ventricle by autotomography. The plastic-canvas "hat" is secured by a strap under

the patient's chin, which helps to keep the head extended. (B) Autotomogram showing gas outlining the anterior end of the third ventricle, the chiasmatic cisterns and their relationship to the pituitary fossa. (Film is viewed in erect position—note the fluid levels in the third ventricle and both lateral ventricles just behind the foramina of Monro.)

ADVANTAGES AND TECHNIQUE

Although designed specifically for autotomography, the apparatus has come to be used routinely for all lumbar pneumograms, since it has unexpectedly solved the problem of maintaining the correct position of the head while the patient is sitting upright and the air is being injected. Neither manual support nor a head harness attached in some other fashion to the body supporter (of whatever type) appears to be as efficient, or sturdy, or acceptable to the patient as this plastic-canvas "hat" hitched to the skull table—the very object to which the position of the head must be kept in a constant relationship.

Concerning the use of the apparatus for autotomography, it can be stated that it enables a completely inexperienced assistant to be reasonably sure of producing a satisfactory result on his first attempt, and without being exposed to direct beam irradiation in doing so. Moreover, it eliminates the uncertain atmosphere of experimentation that so often accompanies the

introduction of a new technique.

The versatility of the apparatus is such that it is of equal value in three recognized positions:

(1) The patient erect, with the head bent forward and the chin tucked in, to demonstrate the fourth ventricle, the aqueduct of Sylvius and the posterior end of the third ventricle (Fig. 2, A and B). It is usually after the first 8 cc. of gas has been injected through the lumbar puncture needle and the scout roentgenograms have been viewed, that autotomography is decided upon. A diaphragm (and preferably a cone) to include no more than the torcular Herophili and the tuberculum sellae is used and the roentgen-ray beam is centered to the external auditory meatus. The maneuver is best performed *immediately* after an additional 5–8 cc. of gas is injected.

(2) The patient prone, usually following ventriculography but also after lumbar encephalography when the fourth ventricle was not seen "on the way up."

(3) The patient supine, with "hanging

head" to raise the level of, and capture air in, the anterior end of the third ventricle (Fig. 3, *A* and *B*). This position is essential for adequate visualization of the optic and infundibular recesses.

Suggested technical factors to be used are 50-55 kv., 50 ma., and 3 seconds.

SPECIFIC APPLICATIONS

The uses of autotomographic techniques in air studies are well known. The advantages of this method of investigation over other methods, particularly conventional tomography, in investigating the midline structures of the skull base have perhaps not been sufficiently emphasized.

AIR STUDIES

(1) Well-pneumatized mastoid air cells may completely obscure the fourth ventricle in the lateral projection or may render its boundaries uncertain. Stereoscopic films or conventional tomography in the horizontal lateral plane are bizarre alternatives to the infinitely simpler technique of autotomography.

(2) Distortion of the aqueduct of Sylvius, or disruption of its normal relationship to the third ventricle above it and the fourth ventricle below it, may not be demonstrable on conventional air studies and may require autotomography to show the whole of this part of the ventricular system. For instance: (a) pontine space-occupying lesions will displace all three structures in a gentle sweep away from the clivus; or (b) the aqueduct of Sylvius may be kinked by a tumor of the superior vermis; these features, obscured on the conventional pneumograms, may be dramatically demonstrated by autotomography.

(3) Overlying air in the cortical subarachnoid channels, in the temporal horns of the lateral ventricles or in the ventral subarachnoid cisterns may completely obscure the outline of the third ventricle, and particularly its vitally important, strategically situated anterior recesses. Since the only satisfactory alternative for the demon-

stration of these structures may be positive contrast ventriculography, it is worthwhile taking pains to obtain a satisfactory autotomogram. A "hanging head" autotomogram may be a dramatic vindication of persistence, and may save the patient an unnecessary operation. Equally valuable is the autotomographic demonstration of a filling defect at the posterior end of the third ventricle due to a pinealoma.

SKULL BASE

A successful autotomogram will show with sharp clarity the image cast by the midline structures, *i.e.*, the sella turcica, the clivus, the margins of the foramen magnum and the atlanto-occipital articulation.

Satisfactory examination of the clivus, either by routine lateral projections or by conventional tomographic cuts made in the true lateral plane, may be impossible if the mastoids are sclerotic. Since erosion of the clivus is best assessed in profile views, autotomography may well offer the best means at our disposal for visualizing the midline part of this structure, from the sella turcica to the anterior rim of the foramen magnum.

Most patients with bony deformities at the craniovertebral angle, including basilar impression, eventually undergo multiple section tomography. A single midline cut, expeditiously and competently performed at the same time as the routine study, may yield sufficient information to enable a diagnosis to be made and to obviate further roentgen examination.

SUMMARY

1. A simple head-holding device for attachment to a craniograph or to a conventional roentgen-ray table is described. The apparatus, primarily designed rigidly to control autotomographic maneuvers with less exposure to the operator, has been found to be useful for holding the patient's head in the correct position during pneumoencephalography.

2. Autotomographic techniques and in-

dications for them are described in relation to the apparatus, and a comparison is made with the more established radiodiagnostic methods.

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PRIMARY SPINAL TUMORS: A SEVEN-YEAR STUDY*

By ARTHUR S. TUCKER, M.D., BISAMAI ARAMSRI, M.D.,
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PRIMARY spinal tumors originate predominantly from nervous tissue and its investments, whereas tumors in the intracranial cavity originate more frequently from the brain than from the meninges and nerve roots. Apparently, this is because the amount of nerve tissue within the brain is greater in proportion to the nerve roots and meninges than it is in the spinal cord. In other words, the occurrence of gliomas, neurofibromas, and meningiomas within the cranium and spinal canal is roughly proportional to the relative volume of nerve tissue, which gives rise to these tumors. Adson¹ reports that spinal tumors arising in the meninges, nerve roots, blood vessels, and supporting tissues outnumber tumors arising within the spinal cord by 4 to 1.

MATERIAL

Primary spinal tumors were found in 96 patients seen in the Cleveland Clinic during the seven years, 1949 to 1955, inclusive. To these have been added 71 cases of tumors of the spinal cord previously seen at the Cleveland Clinic and reported in 1949 by Hannan, Hughes, and Mulvey.⁵ Operations were performed on 165 of the combined 167 total tumor patients. Histologic identification was obtained in 162 cases; the remaining 3 were instances of intramedullary tumors, in which the surgeon hesitated to perform an adequate biopsy for fear of increasing the patient's neurologic deficit. Biopsy of one of these was reported by the pathologist as "tissue insufficient for diagnosis," of another as merely "hyaline fibrous tissue." In the third no biopsy was attempted. Grossly, all 3 were considered to be gliomas.

Our findings have been carefully com-

pared with those described by other authors. The largest series found in the literature was that of Rasmussen, Kernohan, and Adson,⁷ who gave a very detailed account of 557 histologically verified neoplasms of the spine and found another 64 intramedullary lesions which were not identified by biopsy but which were "presumably tumors or cysts of the spinal cord."

The histologic classification in our series, as well as that of Hannan, Hughes, and Mulvey,⁵ is given in Table I. Neurofibroma was the most frequently encountered tumor, and meningioma a close second. However, in our series, 2 tumors listed as neurofibroma were not verified, although the clinical signs and roentgenograms (including, in one instance, a myelogram)

TABLE I
HISTOLOGIC CLASSIFICATION OF PRIMARY SPINAL
TUMORS

	Present Series	Hannan <i>et al.</i> ⁵	Combined Cleveland Clinic Cases
Neurofibroma	27	30	57
Meningioma	25	22	47
Ependymoma	5	10	15
Glioma	10	6	16
Cyst	2		2
Mixed (teratoma)	3	2	5
Lipoma	1		1
Vascular tumors	3	1	4
Chordoma	6		6
Giant cell tumor	1		1
Aneurysmal bone cyst	1		1
Sarcoma	4		4
Lymphoma	8		8
Totals	96	71	167

* From the Departments of Radiology and Neurosurgery, The Cleveland Clinic Foundation, and the Frank G. Bunts Educational Institute.

TABLE II
ANATOMIC DISTRIBUTION OF PRIMARY SPINAL TUMORS

	Cervical Region	Thoracic Region	Lumbar Region	Sacrum	Total
Present series	21	52	19	4	96
Neurofibroma	5	14	8		
Meningioma	3	21	1		
Ependymoma	2	1	2		
Glioma	5	4	1		
Hannan <i>et al.</i> ⁵	16	29	25	1	71
Combined Cleveland Clinic Series	37 (22%)	81 (48%)	44 (26%)	5 (3%)	167
Rasmussen <i>et al.</i> ⁷	100 (18%)	304 (54%)	117 (21%)	35 (7%)	556
Grant ⁴	24 (22%)	70 (65%)	6 (6%)	8 (8%) Cauda	108
Horrax <i>et al.</i> ⁶	12 (20%)	35 (57%)	14 (23%)		61

were typical. These 2 patients refused surgical treatment.

The present study differs from that of Hannan, Hughes, and Mulvey⁵ in that it includes a number of tumors originating outside the spinal canal. These chordomas and bone tumors have been added because the symptoms produced by their pressure upon the spinal cord or its nerves are indistinguishable from those caused by tumors originating within the spinal canal. The cases listed as sarcoma or lymphoma would ordinarily be classified as metastatic tumors, but in each of these instances no primary source elsewhere in the body could be found, and all behaved like primary tumors of the spinal cord.

ANATOMIC DISTRIBUTION OF TUMORS

In approximately one-half of the combined Cleveland Clinic cases, the spinal tumors were found in the thoracic region, which of course constitutes the longest portion of the spinal column. Table II shows the anatomic distribution in our series and in those of several other authors, all of whom reported even a higher preponderance of thoracic lesions.

The relative incidence of all spinal tu-

mors except ependymomas was likewise highest in the thoracic region; this was especially true for meningiomas which exhibited an incidence of 84 per cent. Rasmussen, Kernohan, and Adson⁷ reported 82 per cent of 140, Bull² 92 per cent of 59, and Horrax, Poppen, Wu, and Weadon⁶ 70 per cent of 24 meningiomas as originating in the thoracic region. It is conceivable that the multiple connections and attachments which occur between the pia and arachnoid over the cervical and thoracic portions of the spinal cord may constitute a predisposing factor. In the lumbar spine, by contrast, the pia and arachnoid are completely separated, and here meningiomas occur but rarely. Meningiomas in the sacral portion of the spinal canal to our knowledge have not been seen.

The location of the tumors relative to the spinal cord is given in Table III. A total of 61 per cent of the tumors seen at the Cleveland Clinic were intradural but extramedullary—which is the same percentage as reported by Rasmussen, Kernohan, and Adson.⁷ Most of the neurofibromas and, especially, meningiomas fell into this category. Except for ependymomas, all gliomas were intramedullary.

TABLE III
LOCATION OF PRIMARY SPINAL TUMORS IN RELATION TO SPINAL CORD

	Extradural	Intradural	Intramedullary	Total
Present series	32	53	11	96
Neurofibroma	5	20		
Meningioma	3	22		
Ependymoma		4	1	
Glioma			10	
Hannan <i>et al.</i> ⁵	11	48	12	71
Combined Cleveland Clinic	43 (26%)	101 (61%)	23 (14%)	167
Rasmussen <i>et al.</i> ⁷	196 (36%)	339 (61%)	64 (22%)*	557

* There were 64 additional intramedullary lesions, "presumably tumors or cysts of the spinal cord," which were not identified by biopsy.

A comparison of the distribution of the tumors as to type between the present series and that of Rasmussen, Kernohan, and Adson⁷ is given in Table IV.

AGE AND SEX INCIDENCE

The youngest patient in our series was a boy, six years of age, with a fatty tumor associated with a congenital incomplete formation of the sacrum. The oldest patient was a man, eighty-seven years old, with a neurofibroma at T-12.

TABLE IV
DISTRIBUTION OF PRIMARY SPINAL TUMORS
AS TO TYPE

	Present Series	Rasmussen <i>et al.</i> ⁷
Neurofibroma	27 (28%)	163 (26%)
Meningioma	25 (26%)	140 (23%)
Ependymoma	5 (5%)	160 (26%)
Glioma	10 (10%)	
Cyst	2 (2%)	33 (5%)
Mixed (teratoma)	3 (3%)	
Lipoma	1 (1%)	47 (8%)
Vascular	3 (3%)	
Chordoma	6 (6%)	23 (4%)
Giant cell tumor	1 (1%)	
Aneurysmal bone cyst	1 (1%)	
Sarcoma	4 (4%)	55 (9%)
Lymphoma	8 (8%)	
	96	621

Bull² reported a significant age difference in patients with neurofibromas and meningiomas. Although he found considerable overlap of ages, the average age of his 52 neurofibroma patients was thirty-eight, of his 59 meningioma patients fifty. A similar difference, although not so striking, was noted in our series. The peak age incidence for both meningiomas and neurofibromas was in the sixth decade (Table v). Ependymomas and other gliomas tended to occur in a younger age group.

Previous studies have shown that spinal neoplasms occur more often in females than in males. This has also been the case in our series (Table vi). Horrax, Poppen, Wu, and Weadon⁶ reported twice as many female as male patients among the 61 neurofibromas and meningiomas they collected in a fourteen year period, but did not mention the actual sex incidence in each of the two tumor groups. Bull² reported no marked sex difference among 52 neurofibroma patients, but an 85 per cent female preponderance among 59 patients with meningiomas. Similarly, we have found an almost equal sex distribution among our 25 patients with proved neurofibromas, and 80 per cent of our meningioma patients were females.

SUMMARY

1. By adding our study of 96 cases of spinal tumors seen at the Cleveland Clinic

TABLE V
AGE INCIDENCE OF PATIENTS WITH SELECTED PRIMARY SPINAL TUMORS

Age (yr.)	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Neurofibroma			3	7	1	9	6		1
Meningioma				2	3	11	3	6	
Ependymoma			1	2		2			
Glioma	1	2	2	2	1	1	1		

TABLE VI
SEX INCIDENCE IN PATIENTS WITH PRIMARY SPINAL TUMORS

	Males	Females	Total
Hannan <i>et al.</i> ⁵	27	41	68
Present series	43	53	96
Neurofibroma	13	12	25
Meningioma	5	20	25

during the years 1949 to 1955, inclusive, to a previous study made at the Clinic and reported in 1949 by Hannan, Hughes, and Mulvey,⁵ we have obtained a series of 167 cases of primary spinal tumors for comparison with other studies.

2. Almost one-half of the total tumors were located in the thoracic spine. Five out of 6 meningiomas were in this region; no tumors were found in the sacrum.

3. Sixty-one per cent of the combined total tumors were intradural but extramedullary.

4. Neurofibroma was the most frequently encountered primary spinal tumor; followed by meningioma. These tumors account for approximately one fourth of all spinal tumors.

5. The peak age incidence of patients with neurofibromas and meningiomas was

between fifty and sixty years. Ependymomas and other gliomas tended to occur at an earlier age.

6. The sex difference was not significant except in cases of meningiomas, where 4 out of 5 patients were females.

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BRONCHOGENIC CARCINOMA*

A COMPARATIVE STUDY OF THE PALLIATIVE EFFECTS OF RADIATION THERAPY, RADIATION THERAPY PLUS NITROGEN MUSTARD, AND RADIATION THERAPY PLUS AMETHOPTERIN AND ACTINOMYCIN D IN COMBINATION

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THE first recorded case of bronchogenic carcinoma dates back to a century and a half ago when Bayle³ described the clinical and autopsy findings in one of his patients. An obviously rare condition then gradually and steadily has become the most frequent of all cancers^{12,13,16} and the only form of cancer that is increasing in both sexes.²⁵

It is generally conceded that the surgical removal of the primary tumor and regional lymph nodes and lymphatics is the treatment of choice in operable cases of lung cancer. From 20^{8,18} to almost 50 per cent²⁵ of the cases, depending on the series, are deemed inoperable by the time the patient presents for surgery. Of those patients who do undergo a thoracotomy, about 43 per cent have nonresectable cancer.⁹

What then is available to this majority of lung cancer patients who cannot benefit from surgical extirpation? Even as far back as the early 1930's radiation therapy was used to induce local tumor regression, relieve symptoms and prolong survival time in some patients.¹⁷ Smart and Hilton³¹ reported a 33 per cent five year cure in patients with operable bronchial carcinoma treated by external irradiation alone. These cases, however, are exceptional rather than the rule since most workers treat far advanced inoperable patients in whom the objective of treatment is palliation. More recently, the use of interstitial irradiation

with radioactive iridium has been used with interesting results.⁹

Effective relief of symptoms such as dyspnea, hemoptysis, cough, pain and anxiety, and objective regression of lung tumors and pleural effusions in some cases have been noted with the systemic use of chemotherapeutic agents.^{5,19,20,27,28} These effects are generally transient in nature.

The use of a drug in conjunction with radiation therapy in an attempt to sensitize tumor cells to roentgen or gamma rays has been the subject of many investigations.^{1,23,29} This report compares the clinical effects of radiation therapy alone with those of radiation therapy plus nitrogen mustard, and radiation therapy plus amethopterin-actinomycin D in combination on patients with demonstrable advanced carcinoma of the lung and bronchus.

MATERIAL AND METHODS

One hundred and twelve patients with carcinoma of the lung and bronchus were selected for treatment and observation between 1955-1960. Active treatment extended through 1959 only. All of the patients were declared inoperable or were found to have nonresectable lesions by the surgical staff. All had a cytologic diagnosis established by thoracotomy biopsy, bronchial biopsy, scalene lymph node biopsy, or by exfoliative cellular studies. All pa-

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tients had demonstrable and measurable disease for periodic objective evaluation. Patients excluded from the study were those who because of severe debilitation and extent of disease could not complete even an accelerated course of irradiation and those who because of advanced disease, central nervous system involvement, poor hepatic or renal function, and inanition obviously could not tolerate four to six weeks of intensive chemotherapy.

The ages ranged from twenty-seven years to seventy-eight years with over 90 per cent of the patients above the age of fifty.

The patients were classified into the following therapeutic groups: Group I—radiation therapy alone, 58 patients; Group II—radiation therapy plus nitrogen mustard, 15 patients; and Group III—radiation therapy plus amethopterin-actinomycin D combination, 39 patients.

The majority of patients in the first two groups received treatment according to conventional clinical patterns from January, 1955 to December, 1957 and prior to the institution of experimental radiation therapy plus amethopterin-actinomycin D combination. The physical factors of radiation therapy were: 200–250 kv.; half value layers of .9 and 1.9 mm. of copper; 50 cm. target skin distance; and tumor doses of 1,200–3,000 r in 8–15 days to 8,000 r in 70–90 days.

Nitrogen mustard (methyl-bis [beta-chloroethyl] amine hydrochloride) was given during the roentgen irradiation. A single dose intravenously of 0.4 mg. per kg. of body weight was administered, or the same dose was used but divided equally into two or four daily single injections. In most instances the drug was given at the onset of roentgen therapy. In a few cases, however, it was administered near the end of the course; although the preferred method was to use the drug at the institution of therapy. It was hoped that this alkylating agent given in conjunction with roentgen therapy would produce augmented radiation damage to tumor cells.

Amethopterin (methotrexate) is a folic acid antagonist. This antimetabolite inhibits the enzymatic synthesis of folic acid to folinic acid which acts as a carrier of an essential carbon fragment in the production of nucleic acid. Nucleic acid is necessary for the proliferation of cells. Amethopterin was given in daily doses of 2.5 mg. orally during the first ten days of roentgen therapy with the hope that Paterson's²⁶ therapeutic ratio of tumor tissue would be increased relative to normal tissue.

Actinomycin D is an antibiotic possessing antitumor activity.¹⁴ It potentiates the reaction of radiation upon normal skin and, in some instances, the therapeutic effect of radiation on certain solid tumors.^{2,10,15,21,33} When used in conjunction with amethopterin and one of the polyfunctional alkylating agents, it produces a synergistic or additive effect superior to that of either drug used alone on cancers of testicular origin.^{21,22} Actinomycin D was administered intravenously in doses of 0.5 mg. daily from the sixth to the tenth day of roentgen therapy.

Because of the obvious toxic effects of the drugs employed in the combined radiation therapy plus methotrexate-actinomycin D group, such as depression of bone marrow, oral ulceration, diarrhea, extensive skin epilation over the irradiated areas, and nausea and vomiting, daily appraisal of the clinical status of the patients was essential before each dose of drugs was given. Upon the appearance of toxic manifestations, drug and radiation therapy was discontinued immediately. Appropriate nursing care and adequate nutritional and fluid balance were maintained in each patient who developed toxic symptoms.

The degree of response to treatment in all three groups was based on objective roentgenographic findings and measurement of palpable tumors according to the following criteria: 1+—30 to 50 per cent tumor regression; 2+—50 to 80 per cent tumor regression; 3+—80 to 100 per cent tumor regression; and 4+—no evidence of local or distant disease.

Survival time from completion of therapy

TABLE I
RESULTS OF RADIATION THERAPY (GROUP I)

Sub-Group	Tumor Dose (r)	Time, (da.)	No. of Cases	Objective Response					No. of Cases with Objective Responses	No. of Cases with Subjective Responses	Mean Survival Time (wk.)	Post Therapy Survival Time (wk.)
				0	1+	2+	3+	4+				
I	1,200--3,000	8-15	18	14	2	2	0	0	4/18 (22%)	4/18 (22%)	48	20
II	2,000--3,000	16-29	2	1	0	0	1	0	1/2 (50%)	0/2 (0%)	45	15
III	3,000--5,000	30-50	10	7	1	2	0	0	3/10 (30%)	3/10 (30%)	49	21
IV	3,000--5,000	90	4	3	0	0	1	0	1/4 (25%)	1/4 (25%)	70	26
V	5,000--8,000	50-70	11	10	0	0	1	0	1/11 (9%)	6/11 (54%)	79	34
VI	6,000--8,000	70-90	13	13	0	0	0	0	0/11 (0%)	4/13 (30%)	56	24
Total Cases			58	48	3	4	3	0	10/58 (17%)	18/58 (31%)		

was used as the major criterion for the evaluation of the three methods of treatment. To some extent subjective improvement of symptoms was considered.

RESULTS

The results observed in these 112 patients are shown in Tables I to IV and the comparative survival times are shown in Figure 1. Measurable diminution in the size and extent of lesions was noted on roentgenograms and by palpation in 17 per cent of those treated by radiation therapy alone, in 53 per cent of those treated with radiation therapy plus nitrogen mustard, and in 64 per cent of those patients treated with radiation therapy combined

with amethopterin-actinomycin D. The average total objective improvement in the three groups was 44.8 per cent.

Subjective responses were noted in 31 per cent of the radiation therapy alone group, in 60 per cent of the radiation therapy plus nitrogen mustard group, and in 74 per cent of the radiation therapy plus amethopterin-actinomycin D group. The average total subjective improvement in all three groups was 55 per cent. Subjective responses were based on relief of chest pain, dyspnea, cough, hemoptysis and symptoms referable to superior vena cava obstruction. The duration of relief of symptoms, however, was relatively short and ranged mostly from one to five months with 80 per cent of

TABLE II
RESULTS OF RADIATION THERAPY PLUS NITROGEN MUSTARD—0.4 mg./kg.
OF BODY WEIGHT (GROUP II)

Sub-Group	Tumor Dose (r)	Time (da.)	No. of Cases	Objective Response					No. of Cases with Objective Responses	No. of Cases with Subjective Responses	Mean Survival Time (wk.)	Post Therapy Survival Time (wk.)
				0	1+	2+	3+	4+				
I	1,200--3,000	8-21	10	4	5	1	0	0	6/10 (60%)	7/10 (70%)	54	26
II	2,000--3,000	30-50	2	1	1	0	0	0	1/2 (50%)	0/2 (0%)	33	14
III	3,000--5,000	30-50	3	2	1	0	0	0	1/3 (33%)	2/3 (66%)	36	15
Total Cases			15	7	7	1	0	0	8/15 (53%)	9/15 (60%)		

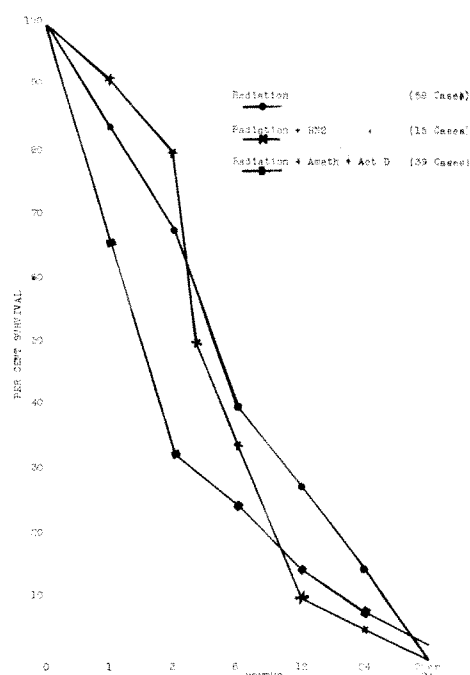


FIG. 1. Comparative survival times after therapy completion.

the patients dying before six months. It is significant that the group of radiation therapy plus amethopterin-actinomycin D treated patients had the largest number of short term objective and subjective responses. The only living patient with no evidence of local or distant disease in this series of 112 patients is from this group also.

All of the patients who received radiation therapy alone or radiation therapy plus nitrogen mustard are dead. The longest survivor (A. S.) of the first group lived

36 months after apparent onset of disease and 24 months after completion of treatment. The longest survivor (W. B.) of the latter group lived 21 months after treatment. Of the radiation therapy alone group, 7 survived over one year, 3 over eighteen months, and none over two years. One of these (P. C.), who had an adenocarcinoma which showed a 3+ objective response, survived 44 months after apparent onset of disease and 19 months post therapy (Fig. 2, *A* and *B*).

Of the 112 patients 12 survived longer than 1 year (Fig. 3, *A*, *B* and *C*), and one still lives. This patient (Y. M.) had an anaplastic carcinoma involving the left upper lobe, pericardium and mediastinum, and which also was adherent to the sternum. This patient has no evidence of disease 31 months after completion of treatment and 36 months after onset of symptoms (Fig. 4, *A*, *B* and *C*).

As noted in Figure 1, the 50 per cent survival time for the radiation therapy alone group is five months, for the radiation therapy plus nitrogen mustard group four months, and for the radiation therapy plus amethopterin-actinomycin D group two months. Within the first group the longest survivors were among those 11 patients (Table I, sub-group v) treated with open ports or with grid to 5,000–8,000 r tumor dose in 50–70 days. Yet, of these, 10 showed no objective response on roentgenograms. Also of interest is the fact that those patients who were treated rapidly to skin tolerance doses in 8–15 days because of far

TABLE III
RESULTS OF RADIATION THERAPY PLUS AMETHOPTERIN-ACTINOMYCIN D (GROUP III)

Sub-Group	Tumor Dose (r)	Time (da.)	No. of Cases	Objective Response					No. of Cases with Objective Responses	No. of Cases with Subjective Responses	Mean Survival Time (wk.)	Post Therapy Survival Time (wk.)
				0	1+	2+	3+	4+				
I	2,000–	10–30	1	1	0	0	0	0	0/1 (0%)	1/1 (100%)	95	88
II	3,000–		38	13	8	8	8	1	25/38 (65%)	28/38 (73%)	55	24
	4,000	30										
Total Cases			39	14	8	8	8	1	26/39 (64%)	29/39 (74%)		

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Sub-Group	Tumor Dose (r)	Time, (da.)	No. of Cases	Objective Response					No. of Cases with Objective Responses	No. of Cases with Subjective Responses	Mean Survival Time (wk.)	Post Therapy Survival Time (wk.)
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II	2,000--3,000	30-50	2	1	1	0	0	0	1/2 (50%)	0/2 (0%)	33	14
III	3,000--5,000	30-50	3	2	1	0	0	0	1/3 (33%)	2/3 (66%)	36	15
Total Cases			15	7	7	1	0	0	8/15 (53%)	9/15 (60%)		

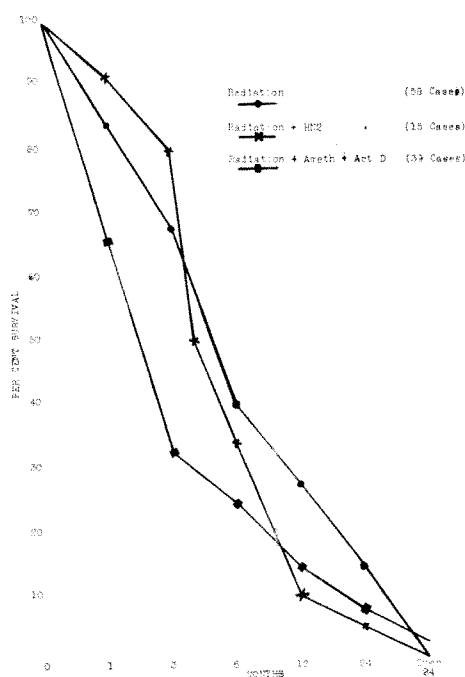


FIG. 1. Comparative survival times after therapy completion.

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TABLE III
RESULTS OF RADIATION THERAPY PLUS AMETHOPTERIN-ACTINOMYCIN D (GROUP III)

Sub-Group	Tumor Dose (r)	Time (da.)	No. of Cases	Objective Response					No. of Cases with Objective Responses	No. of Cases with Subjective Responses	Mean Survival Time (wk.)	Post Therap; Survival Time (wk.)
				0	1+	2+	3+	4+				
I	2,000--	10--30	1	1	0	0	0	0	0/1 (0%)	1/1 (100%)	95	88
II	3,000--											
	4,000	30	38	13	8	8	8	1	25/38 (65%)	28/38 (73%)	55	24
Total Cases			39	14	8	8	8	1	26/39 (64%)	29/39 (74%)		

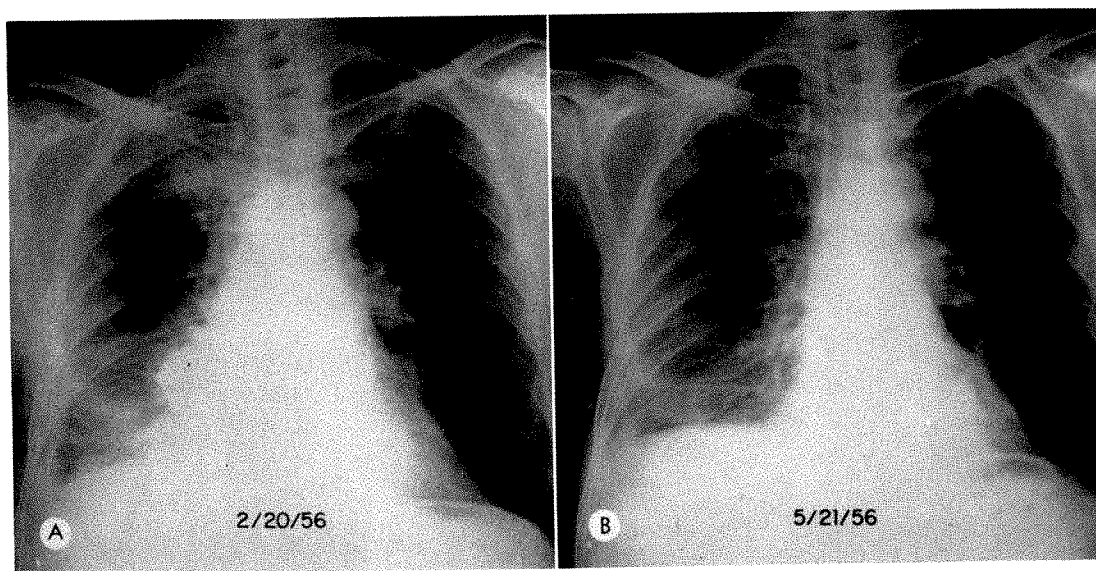


FIG. 2. P. C. (A) Unresectable adenocarcinoma of right upper lung. Roentgenogram made February 20, 1956 prior to radiation therapy alone. Patient received 6,000 r tumor dose in 50 days via open port. (B) Roentgenogram made May 21, 1956, three weeks before completion of radiation therapy. Patient had a 3+ objective response and was asymptomatic 11 months. Patient died 19 months post therapy.

advanced disease, severe symptoms, rib metastases, pleural effusion, superior vena cava syndrome, or severe debility showed a 22 per cent objective response and had a mean survival and post therapy survival of 48 and 20 weeks, respectively.

TABLE IV

POST THERAPY SURVIVAL TIME IN MONTHS BY PATHOLOGIC CLASSIFICATION

	1 Mo.			1-3 Mo.			3-6 Mo.			6-12 Mo.			12-24 Mo.			Over 24 Mo.		
	Rad.	Rad. HN ₂	Rad. A+A	Rad.	Rad. HN ₂	Rad. A+A	Rad.	Rad. HN ₂	Rad. A+A	Rad.	Rad. HN ₂	Rad. A+A	Rad.	Rad. HN ₂	Rad. A+A	Rad.	Rad. HN ₂	Rad. A+A
Squamous Cell Carcinoma (33%)	1	1	—	3	—	2	8	3	1	8	3	1	4	—	1	—	—	—
Adenocarcinoma (9%)	—	—	3	2	—	—	1	1	—	—	—	—	2	1	—	—	—	—
"Malignant Cells" (1%)	—	—	—	—	—	2	—	—	—	—	—	—	—	—	—	—	—	—
Oat Cell Carcinoma (5%)	2	—	—	1	—	—	1	—	—	—	—	1	1	—	—	—	—	—
Anaplastic Carcinoma (52%)	6	—	10	4	2	11	7	3	2	7	1	2	—	—	2	—	—	1
Total	9	1	13	10	2	15	17	7	3	15	4	4	7	1	3	0	0	1

Rad.=Radiation therapy.

Rad. HN₂=Radiation therapy plus nitrogen mustard.

Rad. A+A= Radiation therapy plus amethopterin and actinomycin D.

Of further significance and contrary to general belief, the radiation therapy plus nitrogen mustard group showed shorter survival times than those treated with radiation therapy alone. Also, despite the fact that the radiation therapy plus amethopterin-actinomycin D combination group showed the highest objective and subjective responses, the survival time was the shortest. In addition, there were toxic manifestations, such as, stomatitis, diarrhea, epilation, mild personality changes in some patients, and/or substantial bone marrow depression resulting from this com-

bination therapy. Skin erythema occurred in some patients with as little as 300 r in air. The cutaneous reactions were severe but recovery was relatively rapid. Skin doses of about 3,500–4,000 r produced reactions comparable to those of about 6,000–7,000 r with irradiation alone with conventional rates. Administration of actinomycin D to patients who had received previous irradiation with complete skin recovery caused a reappearance of the skin reaction in some cases. Most of these latter observations have been recorded more fully elsewhere.^{6,10}

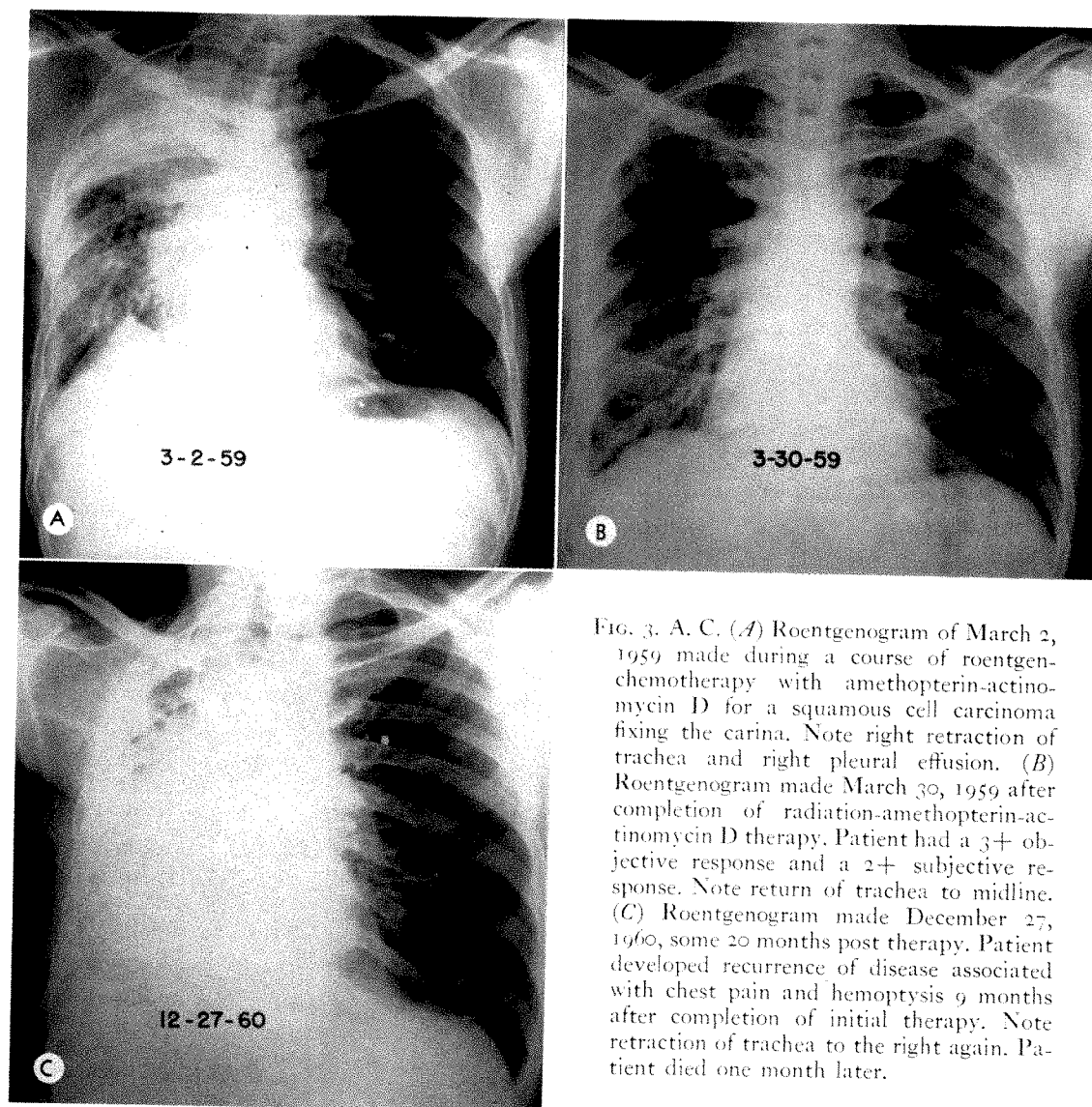


FIG. 3. A. C. (A) Roentgenogram of March 2, 1959 made during a course of roentgen-chemotherapy with amethopterin-actinomycin D for a squamous cell carcinoma fixing the carina. Note right retraction of trachea and right pleural effusion. (B) Roentgenogram made March 30, 1959 after completion of radiation-amethopterin-actinomycin D therapy. Patient had a 3+ objective response and a 2+ subjective response. Note return of trachea to midline. (C) Roentgenogram made December 27, 1960, some 20 months post therapy. Patient developed recurrence of disease associated with chest pain and hemoptysis 9 months after completion of initial therapy. Note retraction of trachea to the right again. Patient died one month later.

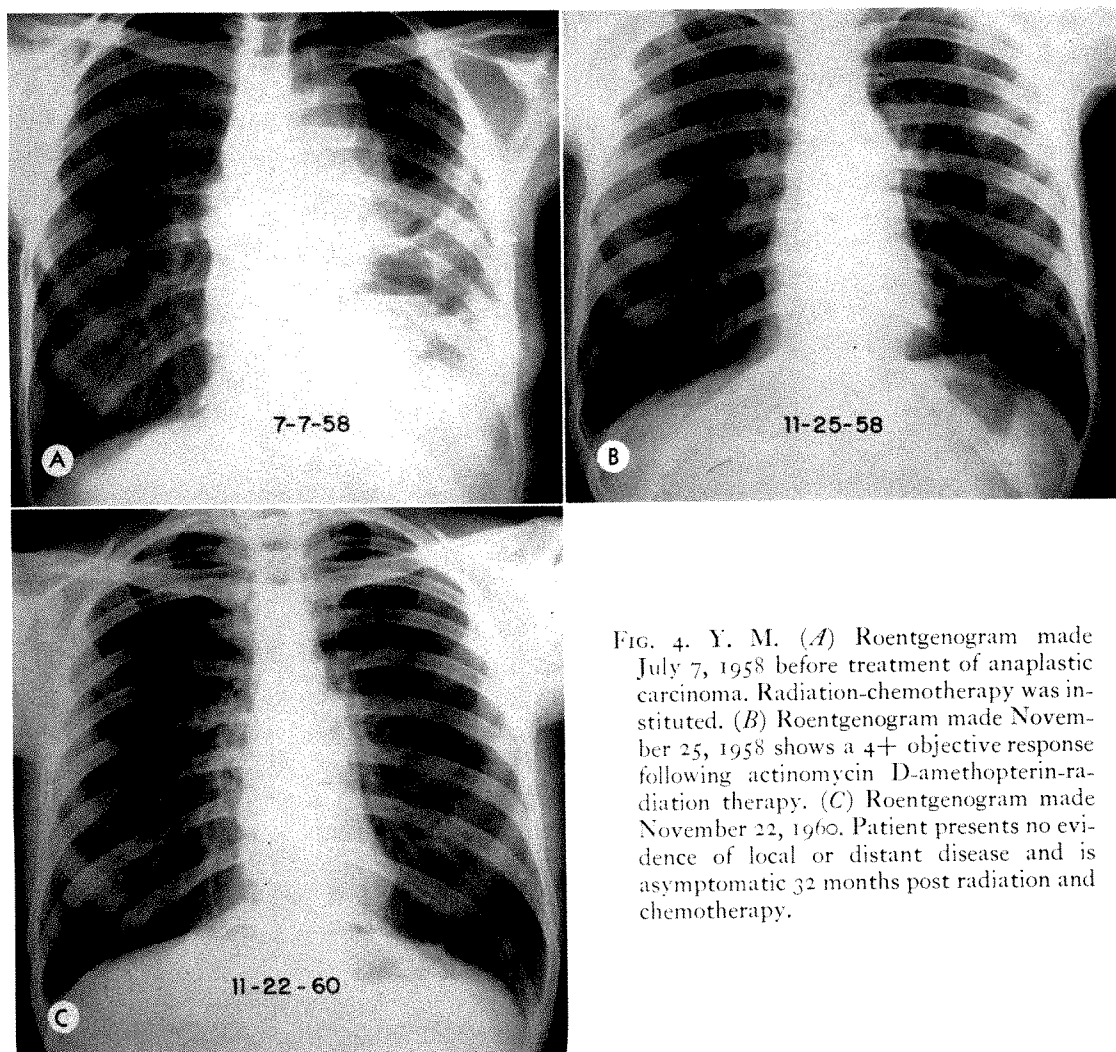


FIG. 4. Y. M. (A) Roentgenogram made July 7, 1958 before treatment of anaplastic carcinoma. Radiation-chemotherapy was instituted. (B) Roentgenogram made November 25, 1958 shows a 4+ objective response following actinomycin D-amethopterin-radiation therapy. (C) Roentgenogram made November 22, 1960. Patient presents no evidence of local or distant disease and is asymptomatic 32 months post radiation and chemotherapy.

DISCUSSION

Five year cures in cases of bronchogenic carcinoma are rare.⁷ It is generally conceded that the average life expectancy from the onset of symptoms to death is about eight months. Of 1,749 cases of lung cancer seen at the Brompton and Royal Marsden Hospitals in London from 1951-1955, the total five year survival rate, after resection, radical or palliative radiation therapy, or after no treatment at all was 6 per cent.⁴ The end-results report at the Fourth National Cancer Conference at Minneapolis (September, 1960) shows 3 and 4 per cent five year survivals for males and females with cancer of the lung and bronchus be-

fore 1950, and a corresponding 4 and 8 per cent after 1950.³² This increase may be due to earlier recognition and diagnosis, changes in therapeutic policy, improved surgical and radiation techniques, and possibly to combinations of radiation therapy with chemotherapy playing an additive and significant role. Here, in this series, as well as in most of the reported ones, the lesions were beyond resection, and the objective of treatment was alleviation of symptoms.

Mention must be made again of the choice of radiation therapy and the dose administered. Unlike chemotherapy in this series, it was not by design. Individual

lesions of varying extent suggested certain types of therapy while the condition of the patient dictated other treatment policies. It would appear to be extremely difficult in far advanced disease states to perform identical surgical procedures on 112 patients. Similarly, all patients with the same condition are not treated identically medically. Radiation medicine and radiation surgery are likewise no different.

In many instances accelerated palliative radiation therapy to skin tolerance was given in an effort to relieve symptoms as quickly as possible with the least distress to the patient. "Eight days" was selected from Paterson's skin tolerance dose chart²⁶ as the most expedient and feasible time. The results have been gratifying. Similar results appear to have been experienced by others.^{11,30}

When grid therapy was employed in the early phases of this series it was felt that the lesion could be encompassed satisfactorily by this method. This, of necessity, required high skin doses at slower rates and longer treatment times. Good results with this method in terms of subjective response and survival should not be attributed to the use of the grid alone but to the time-dose relationship and fractionation since equal results and survivals were obtained in this series with the open port and somewhat similar dose schedules.

Why the 10 patients (Table I, sub-group v) who were treated over comparatively long periods to high total doses with no associated objective responses showed longer survival periods cannot be explained adequately. Since no particular cytologic pathology predominated in this group, it is presumed to be related to better treatment tolerance, less pneumonitis and pulmonary fibrosis, and to time-dose treatment patterns which permit the highest tumor doses possible.

Many authors calculate survival time from onset of symptoms to death. This is a vague procedure and becomes particularly confusing years later when review and tabulation are attempted. Some authors

use dates of admission to the hospital, or dates of initiation of treatment as the beginning of the survival period. Ochsner²⁵ estimates an average delay of 8.7 months from the onset of first symptoms until definitive therapy. This then clearly adds to the survival time. In this series because of the large disparity between treatment times it was felt that the survival time should be measured from the date of completion of therapy. Despite this "shortened" survival time of the patients, the survival rates compare favorably with most reported.

Of interest in these patients is the fact that the group receiving radiation therapy alone had the least morbidity and the best mean survival times with little correlation of objective and subjective responses. If improved results with orthovoltage therapy are to be obtained, the indications are that higher tumor doses must be given.

No statement can be made from patient treatment observations concerning improvement of the therapeutic ratio. This series does present, however, some evidence to suggest that combined radiation-chemotherapy improves objective and subjective responses in some patients with bronchogenic carcinoma.

As a greater variety of new drugs becomes available, further improvement in combination therapy should be possible. In following the theme and proposals of the Fourth National Cancer Conference,⁷ it is hoped that more extensive trials of combined radiation-chemotherapy, including preoperative use, will be instituted.

SUMMARY

One hundred and twelve patients with advanced bronchogenic carcinoma were treated with three modalities; namely, radiation therapy alone (Group I), radiation therapy plus nitrogen mustard (Group II), and radiation therapy combined with amethopterin and actinomycin D (Group III). Of the patients subjected to radiation therapy alone using either rapid palliative therapy to skin tolerances or long term

large total doses, 17 per cent showed objective and 31 per cent subjective responses. Of the patients receiving radiation therapy plus nitrogen mustard, 53 per cent showed objective and 60 per cent subjective responses. Of the patients treated with radiation, amethopterin and actinomycin D in combination, 64 per cent showed objective and 74 per cent subjective responses. The 50 per cent survival time for Group I is five months, for Group II four months, and for Group III two months. In addition, it was noted that radiation in combination with chemotherapy induces augmented but usually reversible toxicity to the gastrointestinal, hematopoietic, and dermatologic systems.

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SIALOGRAPHY OF THE SUBMAXILLARY SALIVARY GLAND

A NEW TECHNIQUE

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SIALOGRAPHY is regarded as a significant diagnostic aid in affections of the parotid and submaxillary salivary glands. The technique for parotid sialography is standardized to a considerable degree and the results are uniformly good in competent hands. However, when submaxillary gland sialography is performed, even by skilled operators, failure is the frequent, if not the usual, result. This can be traced to the anatomic peculiarities of Wharton's duct, which is normally tortuously situated in its bed in the floor of the mouth (Fig. 1 and 2). The parotid duct also has a similar tendency toward tortuosity; however, in parotid sialography the tortuous course of the duct is ironed or stretched out by firm forward manual traction of the cheek. The traction straightens out the duct and allows for easy introduction and passage of a blunt-tipped needle, cannula or small catheter without impingement against the wall of the duct and the resultant accor-

tioning of the duct. When performing submaxillary salivary gland sialography the disposition of the anatomic parts does not allow for traction of Wharton's duct. It is chiefly for this reason that sialography of the submaxillary system frequently fails. It is true that special skill and an assiduous desire to succeed increases the incidence of success, but often after a reasonable trial the effort is abandoned.

METHOD

The purpose of this presentation is to describe a relatively simple method by which to straighten Wharton's duct and thereby achieve uniform success in submaxillary duct sialography. The only way that this can be done is by direct traction

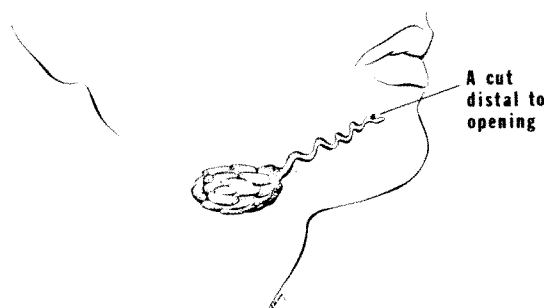


FIG. 1. Diagrammatic sketch showing the normal tortuous course of the submaxillary gland.

of the duct by a forceps (Fig. 2, 3 and 4). A few drops of 2 per cent novocaine with epinephrine are injected into the periductal tissues corresponding to the distal 2.5 cm. portion of the duct. The duct is then grasped near its end by a mosquito forceps and stretched. The taut duct at a point about 1 cm. proximal to its terminal opening is cut transversely about half-way through. This large patulous opening is easily sounded for an adequate distance by a small probe. A cannula or small catheter is then introduced through the opening and inserted 2 to 3 cm. or more, so as to prevent reflux of the radiopaque material. Various modifications of this

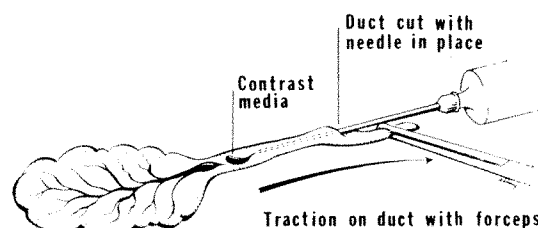


FIG. 2. Diagrammatic sketch showing the needle in the duct which is straightened by traction with forceps.

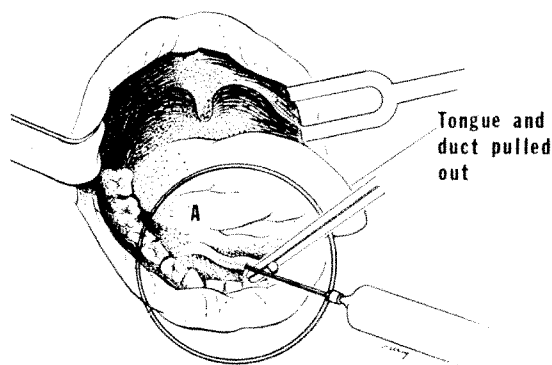


FIG. 3. Diagrammatic sketch demonstrating the duct retracted forward by a mosquito forceps and the needle placed in the cut duct. (The needle is not introduced through the normal opening at the end of the duct.)

technique have been tried; however, the method described here has proved to be the most practical.

Over 50 submaxillary duct sialographies have been performed without adverse complications. Obstruction of the duct did not occur and no postprocedure discomfort was experienced. After completing the procedure it has been the author's practice to prescribe the sipping of lemon juice frequently for about seventy-two hours. The patient is also advised to chew gum. Follow-up roentgenograms are advisable within five days to one week in order to check the emptying of the duct system.

SUMMARY

1. A new technique for the performance

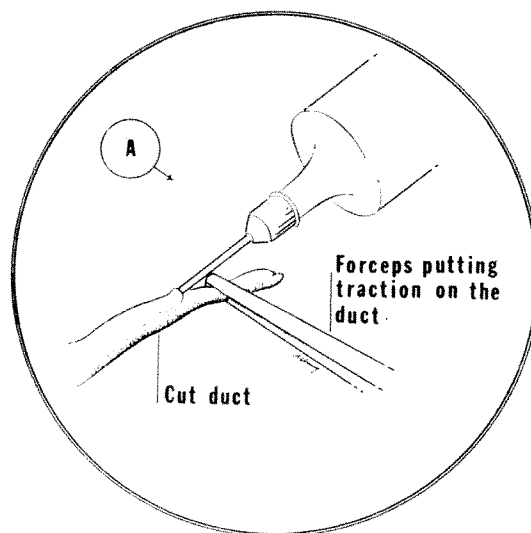


FIG. 4. A. Enlargement of the circled area in Figure 3. Note the needle entering the lumen of the duct distal to its normal opening. A small transverse incision exposes the lumen.

of submaxillary duct sialography is described.

2. With this technique a larger opening is obtained for the easy introduction of the cannula.

3. The technique allows necessary traction for straightening Wharton's duct and thus passage of the cannula without accor-dioning the duct is possible.

4. The procedure is without complications.

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DETAIL VISIBILITY IN RADIOGRAPHS: AN EXPERIMENTAL AND THEORETICAL STUDY OF GEOMETRIC AND ABSORPTION UNSHARPNESS*

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IN A previous paper² the photographic density distribution across the radiographic image of a cylindrical object was calculated for an idealized situation, *viz.*, parallel, monochromatic radiation without scatter. It was demonstrated mathematically that the density gradient at the edge of the image is a function of the geometric configuration and the absorption coefficients of the object and its surroundings, as well as the contrast of the radiographic film. More specifically, it was shown quantitatively that, even in the absence of geometric, screen and movement unsharpness, the partial absorption of x-rays in the object resulted in a lower density gradient at the edge of the radiographic image than would be obtained with a totally absorbing object. In accordance with results obtained from an investigation of photographic images,¹ we assumed that, for radiographic images also, image sharpness is a function of density gradient and we designated the subjective impression caused by this lowering of the density gradient as "absorption unsharpness."

Although this study served well as an introduction to the quantitative understanding of the well-known experimental phenomenon of absorption unsharpness, it was quite unrealistic because parallel (point source at infinity), monochromatic radiation without scatter was assumed for the derivation of the equations. In the present investigation we shall take into consideration the fact that, in practice, we encounter diverging radiation emanating from a source of finite size which may be situated at an arbitrary position relative to the object. Since scatter-free, monochromatic

radiation can be approximated experimentally, as will be shown, it has been possible to test the theoretic results by experiment.

THEORY

A. CYLINDRICAL OBJECT

Consider a point source of monochromatic penetrating radiation placed at a finite distance D from a partially absorbing object with a circular cross section of radius R , as shown in Figure 1. The object with linear absorption coefficient μ is embedded in a medium having negligible absorption (air) and is placed a distance d above the film plane. The source is dis-

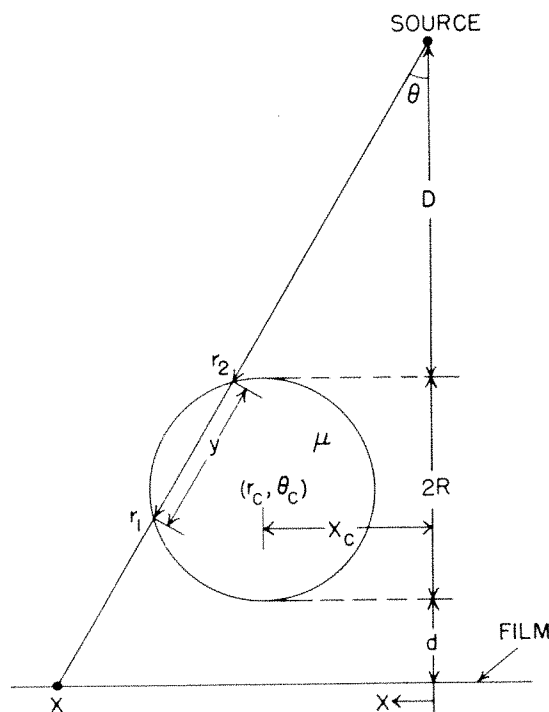


FIG. 1. Point source of x-rays and cylindrical object.

* Communication No. 2152 from the Kodak Research Laboratories, Eastman Kodak Company, Rochester, New York.

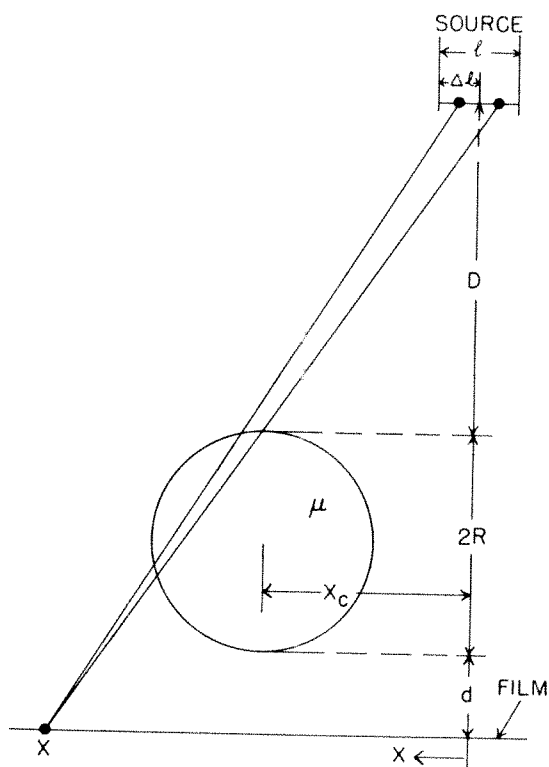


FIG. 2. Extended source of x-rays and cylindrical object.

placed a distance x_c from a line perpendicular to the film plane through the center of the object. If x is a linear co-ordinate measured in the film plane perpendicular to the axis of the cylinder, the radiation intensity arriving at any point x in the film plane is given by

$$I_x = I_0 e^{-\mu y}, \quad (1)$$

where I_0 is the intensity at x in the absence of the partially absorbing object and y is the length of the absorbing path within the object. Note that we have assumed that the dimensions involved are such that the variation of I_0 with the distance from the source, as the point x is moved along the film plane, can be neglected and that the contribution to I_x by radiation scattered in the object is negligible.

The absorbing path length $y(x)$ can best be found with the help of polar co-ordinates. Let the point source be the origin of a polar co-ordinate system (r, θ) , as indi-

cated in Figure 1. Then the equation of the circular circumference of the object is

$$r^2 - 2r r_c \cos(\theta - \theta_c) + r_c^2 = R^2 \quad (2)$$

where (r_c, θ_c) are the co-ordinates of the center. This is a double-valued function of r ; i.e., for a given value of θ two values, r_1 and r_2 , of r result. Then the length y of the absorbing path in the object is given by

$$y = r_1 - r_2 \quad \text{if } r_1 > r_2, \quad (3)$$

as can be seen from Figure 1. Solving equation (2) for r , we find

$$r_{1,2} = r_c \cos(\theta - \theta_c) \pm [r_c^2 \cos^2(\theta - \theta_c) - (r_c^2 - R^2)]^{1/2}$$

and it follows from equation (3) that, for any value of θ ,

$$y = 2[r_c^2 \cos^2(\theta - \theta_c) - (r_c^2 - R^2)]^{1/2},$$

which can be written

$$y = 2[R^2 - r_c^2 \sin^2(\theta - \theta_c)]^{1/2}. \quad (4)$$

In order to test this equation experimentally, it is more convenient to express y in terms of the linear co-ordinate x . Using the identity

$$\sin(\theta - \theta_c) = \sin \theta \cos \theta_c - \cos \theta \sin \theta_c,$$

in conjunction with the following equations found from Figure 1,

$$\begin{aligned} \cos \theta &= \frac{D + 2R + d}{L}; & \sin \theta &= \frac{x}{L} \\ \cos \theta_c &= \frac{R + D}{r_c}; & \sin \theta_c &= \frac{x_c}{r_c} \end{aligned}$$

with

$$\begin{aligned} L &= [x^2 + (D + 2R + d)^2]^{1/2}; \\ r_c &= [x_c^2 + (R + D)^2]^{1/2} \end{aligned}$$

and substituting into equation (4), we obtain

$$y = 2 \left\{ R^2 - \frac{[x(R + D) - x_c(D + 2R + d)]^2}{x^2 + (D + 2R + d)^2} \right\}^{1/2}. \quad (5)$$

This is the expression which is to be substituted into equation (1) for the calculation of the intensity distribution in the

film plane. Thus we can write implicitly

$$I = I_0 e^{-\mu y(x, x_c)}. \quad (6)$$

It will be recalled that equation (5) is valid only for a single point-source. In order to determine, in a rigorous manner, the intensity distribution in the film plane due to a source of finite size, an integration over the area of the source would have to be performed. However, the calculations can be simplified by applying the following approximations.

Let us consider the extended source to be made up of an infinite number of line sources. The gross aspects of the *relative* intensity distribution in the film plane can then be described by means of one of these line sources l which is oriented perpendicular to the edge of the object under investigation, and situated in the plane formed by the perpendicular to the film plane and the line along which the intensity is to be measured. The influence of the remaining line sources, not lying in this plane, on the *relative* intensity distribution would be of secondary importance. However, this still leaves the difficult task of integrating

$$I = \frac{I_0}{l} \int_{-l/2}^{l/2} e^{-\mu y(x, x_c)} dl$$

with $y(x, x_c)$ given by equation (5). The following approximation will eliminate this difficulty.

If the source of finite length l is separated from the object by a distance such that the resulting geometric unsharpness cannot be detected by the observer, we will regard the source as a point source and use equation (5). Applying this basic approximation to the case of a source of length l at an arbitrary distance D from the object, we calculate what elementary length Δl contained in l would give geometric unsharpness which is just not detectable by the observer and substitute a point source for this elementary length Δl . If this is done for every elementary length Δl contained in l , the line source l is replaced by a finite number of point sources separated by distances Δl , as shown in Figure 2. Closer study of Figure

2 will reveal that, for each point source, equations similar to (5) and (6) apply. In particular, for two point sources we have, for the intensity distribution in the film plane,

$$I = \frac{1}{2} I_0 \{ \exp[-\mu y(x - \frac{1}{4}l, x_c - \frac{1}{4}l)] + \exp[-\mu y(x + \frac{1}{4}l, x_c + \frac{1}{4}l)] \} \quad (7)$$

and for three point sources,

$$I = \frac{1}{3} I_0 \{ \exp[-\mu y(x - \frac{1}{3}l, x_c - \frac{1}{3}l)] + \exp[-\mu y(x, x_c)] + \exp[-\mu y(x + \frac{1}{3}l, x_c + \frac{1}{3}l)] \}. \quad (8)$$

It should be noted that we have assumed that the variation of absorption unsharpness with the size of the source is not greater than the variation of geometric unsharpness. The good agreement with experimental results shows that this assumption is justified within the limits of experimental error.

It is not sufficient to describe the radiographic image in terms of the x-ray intensity in the film plane (equations 5-8). The response of the observer depends on the film density and contrast which are, in turn, related to the x-ray intensity by way of the characteristic curve of the film. Thus the image characteristics depend on the type of film used and on the development conditions; in short, on any phenomenon which affects the shape of the characteristic curve. We can write in general

$$D = f(E) = f(Ir), \quad (9)$$

where the functional relationship is given by the characteristic curve of the film. Substitution of equations (5)-(8) in equation (9) yields the density distribution in the image.

B. PLANE PARALLEL PLATE

The fact that diverging radiation is taken into account makes it possible to find the absorption unsharpness of a plane parallel plate situated at an arbitrary position relative to the source of penetrating radiation.

Let us replace the cylindrical object

$$\begin{aligned}
 & + \exp \left[-\mu y_a \left(x_1 + \frac{1}{3}l, x_c + \frac{1}{3}l \right) \right] \} \quad (16) \\
 I_{x_2} = & \frac{1}{3}I_0 \{ \exp \left[-\mu y_b \left(x_2 - \frac{1}{3}l, x_c - \frac{1}{3}l \right) \right] \right. \\
 & + \exp \left[-\mu y_b(x_2, x_c) \right] \\
 & \left. + \exp \left[-\mu y_b \left(x_2 + \frac{1}{3}l, x_c + \frac{1}{3}l \right) \right] \} \right\}.
 \end{aligned}$$

These equations in conjunction with equation (9) will give the density distribution in the image.

EXPERIMENTS

The radiographic objects used to test the theoretical expressions derived in the previous sections were: an aluminum cylinder having a $\frac{1}{2}$ inch diameter and an aluminum plate $\frac{1}{2}$ inch thick. Both objects had carefully machined, smooth surfaces. They were irradiated with strongly filtered 100 kv. x-rays emanating from a 4.5×4.5 mm.² focal spot. With the help of a technique described by Seemann and MacGillivray,³ it was ascertained that a filter of copper, 3 mm. thick, placed between the

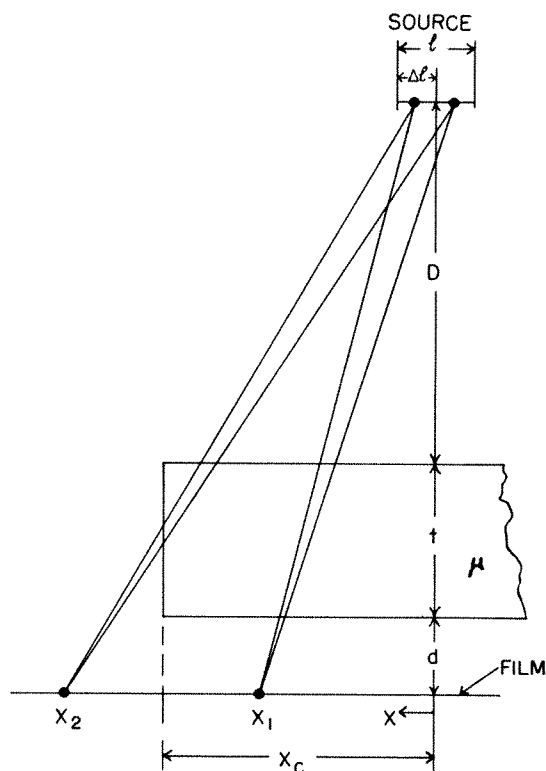


FIG. 4. Extended source of x-rays and plane parallel plate.

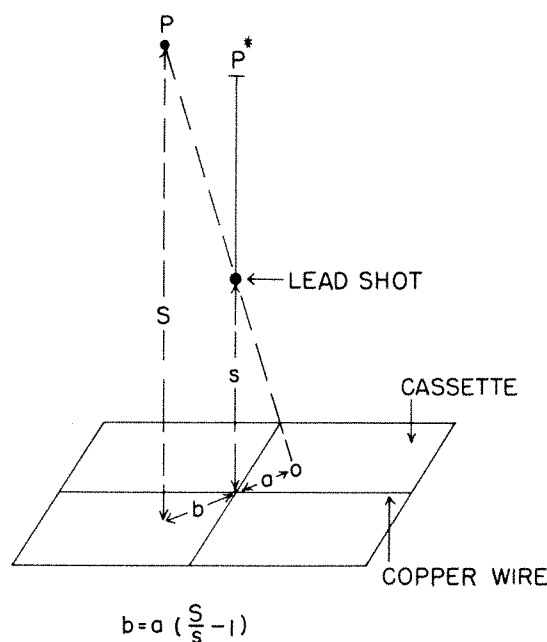


FIG. 5. Positioning of focal spot P.

x-ray tube and the object resulted in nearly monochromatic* radiation and thus in a constant value for the linear absorption coefficient of the aluminum, $\mu = 0.61 \text{ cm.}^{-1}$. Since the amount of scattered radiation reaching the film from the object is a function of, among other factors, the irradiated volume and the distance between object and film, the objects were placed 1 inch away from the film and were shielded with a lead diaphragm so that an area of only $\frac{1}{4}$ by $\frac{1}{2}$ square inch was exposed to the radiation. Under these conditions it was found that the intensity of scattered radiation reaching the film was about 4 per cent of the primary radiation intensity. Thus the condition of monochromatic radiation without scatter, which was the basis for the theoretical derivations, was nearly satisfied.

The position of the focal spot relative to the object was determined by the following method. As indicated in Figure 5, a rectangular co-ordinate system formed by

* The filtered radiation is "monochromatic" or "monoenergetic" only to the extent that additional filtration would not result in a different value for μ . This depends, of course, on the accuracy of the experiment. The relatively narrow band of wave lengths penetrating the filter under these conditions is often called "homogeneous" radiation.

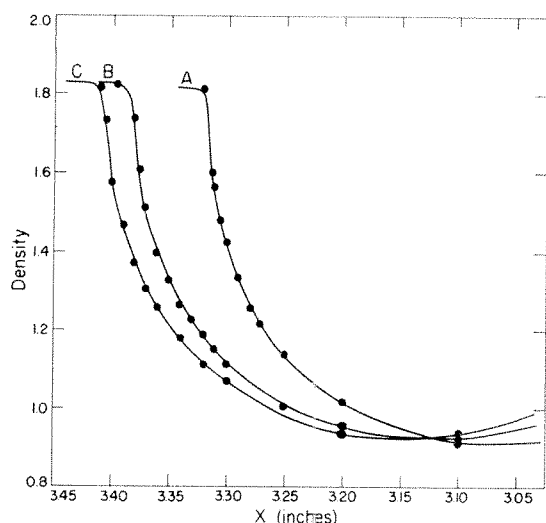


FIG. 6. Microdensitometer tracings across image of cylinder ("noise" smoothed out). ● Calculated values. $x_c = 3.0$ inches; $D_A = 62.5$ inches; $D_B = 31.25$ inches; $D_C = 20.80$ inches.

copper wires was affixed to a film cassette, and a small piece of lead shot was suspended on a thread at a point P^* close to the actual position P of the focal spot. The lead shot and the origin of the co-ordinate system were made to coincide and the lead shot was then raised to a known distance s above the cassette. After an x-ray exposure of this arrangement had been made, the position of the focal spot relative to the co-ordinate system could be calculated from the relative positions of the images of the wires and the lead shot, as shown in Figure 5. Now the focal spot was placed a constant horizontal distance x_c from the test object (cylinder or plate) and exposures were made at three vertical distances D corresponding to the approximations of one, two and three point-sources discussed in the theory.

The images were recorded on Kodak Industrial X-ray Film, Type M, from which one emulsion was removed to minimize the effect of parallax unsharpness due to the thickness of the film base, and to facilitate accurate tracing of the image with a microdensitometer. Over the limited density range encountered in this experiment (0.9–1.9), the response of single-coated Type M

film can be described by

$$D = KE + C$$

so that equation (9) becomes

$$D = KI_0 e^{-\mu y} + C. \quad (17)$$

The resolution of the microdensitometer was adjusted so that the instrument could not detect the geometric unsharpness when the focal spot was at the maximum distance from the object.

RESULTS

Figures 6 and 7 show the microdensitometer tracings obtained from the radiographic images of the cylinder and the plane parallel plate, respectively. The tracings have been smoothed out to eliminate "noise" due to the granularity of the film. The points on the curves are the calculated values of density at distances x measured to the perpendicular from the film plane to the focal spot. Thus it is seen that theory and experiment are in good agreement. An actual microdensitometer tracing similar to curve C in Figure 7 has been reproduced in Figure 8 in order to give an indication of the general noise level.

Proceeding from right to left in each figure, we note that the curves correspond to decreasing vertical distances D between

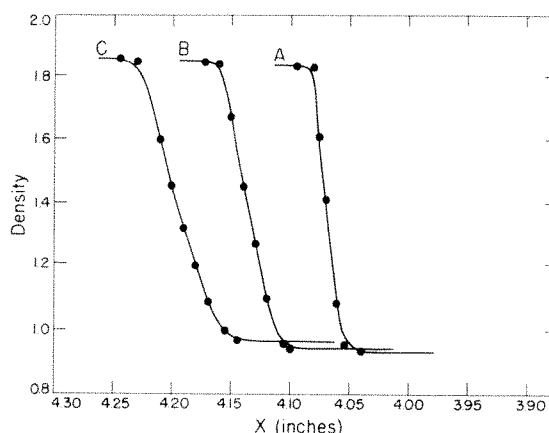


FIG. 7. Microdensitometer tracings across image of plane parallel plate ("noise" smoothed out). ● Calculated values. $x_c = 4.0$ inches; $D_A = 75.0$ inches; $D_B = 38.25$ inches; $D_C = 25.50$ inches.

focal spot and object. The horizontal distance x_c between the object and the perpendicular from the film plane to the focal spot was held constant. Thus the curves show how the radiographic image is shifted in the film plane as the position of the object relative to the focal spot is changed.

Furthermore, it is seen from Figures 6 and 7 that the partial absorption of x-rays in the object causes a continuous change of density in the image, and a decrease of the density gradient at the edge as compared to the infinite gradient which would give the impression of perfect sharpness. The magnitude of this decrease depends on the position of the object relative to the focal spot. The density distributions shown in the figures result in an image unsharpness which increases from right to left.

These results indicate that the theoretical equations derived in this study provide a satisfactory explanation of the physical factors entering into the appearance of absorption and geometric unsharpness in radiography. Therefore, it will be permissible to use these equations in future investigations regarding the objective evaluation of radiographic image quality.

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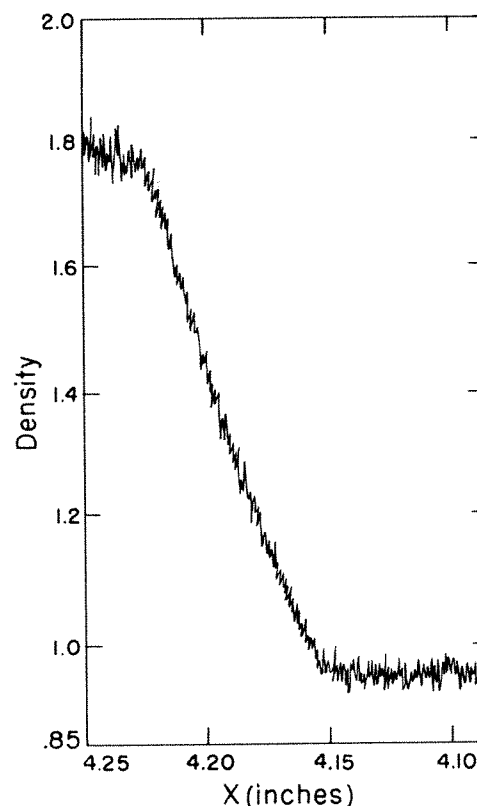


FIG. 8. Microdensitometer tracing across image of plane parallel plate. $x_c = 4.0$ inches; $D = 25.5$ inches.

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DUPLICATION OF ROENTGENOGRAMS BY SOLARIZATION*

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THE duplication of roentgenograms by solarization is an old technique and has been brought to the attention of radiologists in the past.¹⁻³ However, we are impressed that so few radiologists are aware of this very simple method for the adequate reproduction of roentgenograms.

Many radiologists have found Log-Etronic reproductions objectionable because of the alteration in the tonal quality and the necessity of making an intermediate copy so that the final reproduction will be "negative," as is the original roentgenogram. Also, the initial cost of the equipment is considerable. In contrast, the duplication of roentgenograms by solarization can easily be done by anyone with a minimum of equipment and the reproduc-

tion will be an almost exact duplicate of the original (Fig. 1, *A* and *B*).

EQUIPMENT AND METHOD

The equipment needed is: (1) a 14×17 inch printing frame; (2) a reflector flood 2 (standard photoflood); (3) a goose-neck lamp; (4) x-ray film, any brand; and (5) standard x-ray film processing equipment.

The procedure is quite simple and can be done in a dimly illuminated room. A sheet of x-ray film, the same size as the original, is pre-exposed by flashing it with the reflector flood for 1 second. The original roentgenogram is placed in the printing frame and the pre-exposed film is placed in contact with it. The pressure back is firmly secured to assure good contact between the

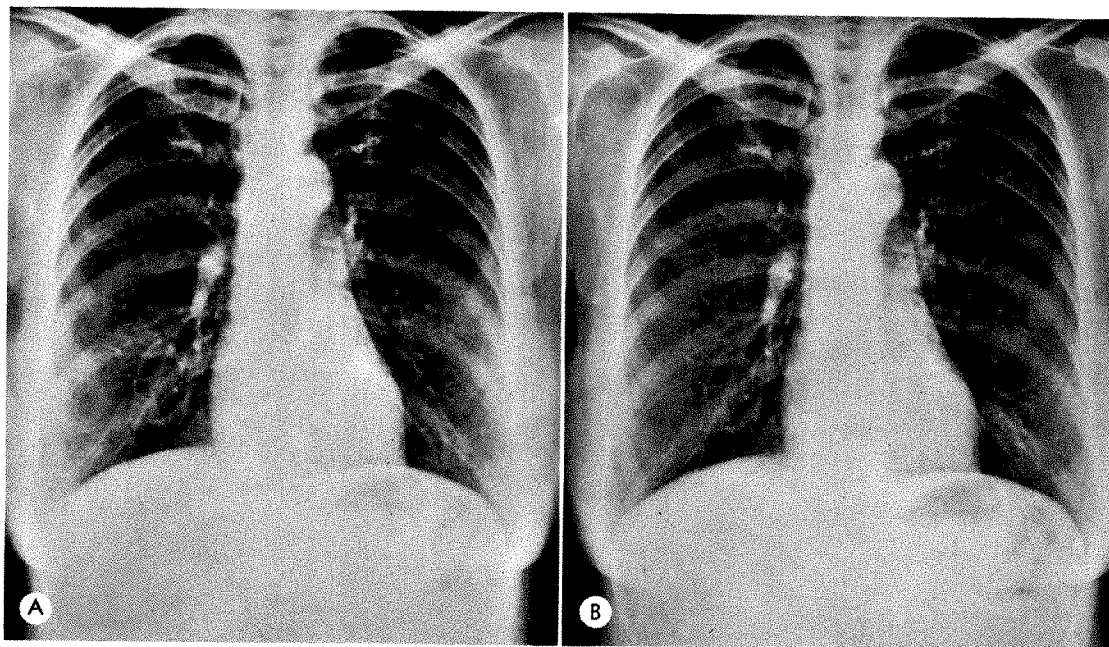


FIG. 1. (*A*) The solarized copy is almost a perfect reproduction of (*B*) the original roentgenogram. Inspection of the chest roentgenograms is necessary to identify the copy and the original.

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two sheets of film. The exposure is then made. We have found that at a 5 foot source-to-frame distance exposure times vary between 10 and 60 seconds. The film is then processed in standard x-ray film solutions. The developing time should be approximately one-half the recommended full development time. Under-development helps to reduce contrast, which is enhanced by any copying technique. Processing can be done in dim white light.

The film used for the reproduction can be a "ruined" x-ray film, *i.e.*, exposed and undeveloped film. The explanation of this lies in the principle of solarization. The log exposure curve of film that radiologists are familiar with is actually incomplete. After reaching maximum density (blackness), the curve returns to minimum density (whiteness). Therefore, a "ruined" film, being pre-exposed to the maximum density level, is equivalent to a fresh film pre-exposed to the maximum density level, since any pre-existing image is "wiped out."

Also, from this exposure curve, if the exposure is incorrect for the reproduction, to make the copy lighter the time of exposure must be increased, and the reverse is true to make the copy darker.

A precaution of great importance is careful handling of the film. Minimal bending of the film used for the reproduction will cause objectionable artefacts that would not have appeared with standard roentgenographic exposures.

We have utilized an adjunctive technique to predetermine exposure time. A densitometer is employed to scan the area of interest on the roentgenogram. Then by trial and error a standard curve of exposure time versus density is drawn and this is used in predetermining exposure times for future copies. A separate curve for chest roentgenograms has been found necessary; all other regions are well incorporated in a single curve. This procedure is not absolutely necessary, since the inherent principle on which the technique is based permits great latitude of exposure and

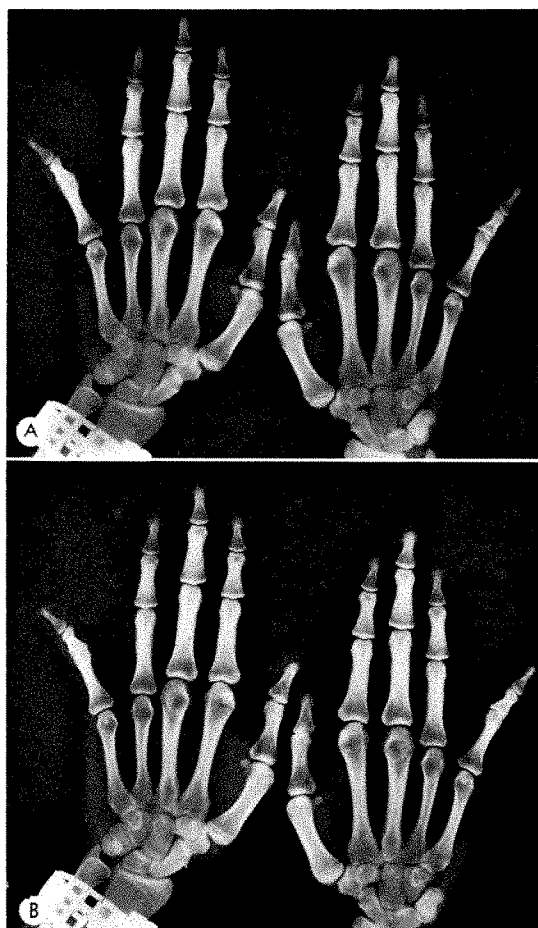


FIG. 2. (A) The solarized copy shows some loss of fine trabecular pattern, as compared to (B) the original hand roentgenogram. However, the copy is quite acceptable.

acceptable copies can be obtained with approximate exposures.

We have found, using a rapid film processor (Pakorol-X), that four times the usual exposure for duplication is necessary for adequate copies.

The duplicate roentgenograms have more contrast than the original and, although they do show a slight reduction in sharpness this has not detracted from their diagnostic worth (Fig. 2, A and B). The loss of sharpness is the result of the double emulsion of the x-ray film. The image is diffused by the support of the film before it reaches the second emulsion. A single emulsion film is available (Gevaert) that should produce

sharper reproductions, since the diffusion of the image is eliminated. However, the advantage of a single emulsion film is not sufficient to warrant substituting it for readily available x-ray film.

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THE AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE

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Representative on the Board of Chancellors of the American College of Radiology: Milford D. Schulz, Boston, Mass.

Forty-fourth Annual Meeting: Waldorf-Astoria Hotel, New York, N. Y., April 2-4, 1962.

* For 1962.

EDITORIAL

RADIATION REGISTRY OF PHYSICIANS

IN A recent editorial in this Journal,¹ which dealt with the leukemogenic and cancerogenic effects of radiation, the opinion was expressed that long-range, carefully compiled, statistical analyses represent important contributions to the study of these effects and that further extensive investigations of all aspects of the radiation hazards are necessary.

It was pointed out that, as regards the leukemogenic effect, the evidence has been drawn chiefly from two fields of observation, both of which apparently have established a positive correlation between incidence of occurrence and irradiation: firstly, the Hiroshima atomic bomb survivors; and secondly, the ankylosing spondylitis radiotherapeutic series.

There is a third field of leukemogenic effect which received considerable attention in the literature, *i.e.*, the occupational exposure of radiologists to roentgen rays and other ionizing radiations. However, the material on this subject is rather inconclusive and to some extent controversial. Warren,² for instance, found that for the period of 1950-1954, the death rate from leukemia for all physicians in the United States was about three times that for the adult population and that a definitely higher percentage was noted in radiologists. In the period 1930-1954, 0.63 per cent of the deaths from specified causes were due to leukemia in nonradiologists as against 2.33 per cent for all specialists in contact with radiation and 3.65 per cent for radiologists. During the same time, the mean age of non-radiologists dying from leukemia was 60 years, as against 55.8 years for radiologists.

In the study of the deaths of the entire group of 82,441 physicians, it was found that radiologists died on the average 5.2 years earlier than did other physicians. March, in a recent report,³ which is an extension of two former ones published in 1944 and 1950, states that the incidence of death from leukemia during the decade of 1949 to 1958 in the United States was about four to five times greater in radiologists than in nonradiologic physicians. This is approximately one-half the differential that existed during the preceding two decades. March anticipates that with improved protection this differential will tend to diminish still further, but will not entirely disappear. On the other hand, Court-Brown and Doll,⁴ in a study of 1,377 living and dead male radiologists of Great Britain for the 60-year period of 1897 to 1956, found only 3 deaths from leukemia, 2 of which occurred prior to 1921. This is less than the expected number of 0.3-0.5 in the general population of similar sex, age and social class distribution prior to 1921, and of 0.7-0.9 after 1921, although the incidence of leukemia is known to have generally increased since then in Great Britain. The Medical Research Council of Great Britain in its First Report issued in 1956,⁵ in referring to the American radiologists states, "that there may well be an increased death rate from leukaemia among American physicians as a whole, compared with the general population, and in particular among American radiologists, but it is not possible to esti-

³ MARCH, H. C. Leukemia in radiologists, ten years later; with review of pertinent evidence from radiation leukemia. *Am. J. Med. Sc.*, 1961, 242, 137-149.

⁴ COURT-BROWN, W. M., and DOLL, R. Expectation of life and mortality from cancer among British radiologists. *Brit. M. J.*, 1958, 2, 181-187.

⁵ The Hazards to Man of Nuclear and Allied Radiations. The Medical Research Council, June, 1956, Cmnd. 9780, H. M. Stationery Office, Atlantic House, Holborn Viaduct, London, E.C. 1, England (Price 5s. 6d net).

¹ LEUCUTIA, T. Leukemogenic and cancerogenic effects of radiation. *AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED.*, 1961, 85, 989-994.

² WARREN, S. Longevity and causes of death from irradiation in physicians. *J.A.M.A.*, 1956, 162, 464-468.

mate the extent of the increase with any certainty." In its Second Report issued in 1960⁶ it adds that, even for the sources cited above, "the risk of developing leukaemia as a result of exposure to radiation may be somewhat less than we assumed in 1956."

The leukemogenic effect, of course, represents only one facet of the long-range radiation hazards, but the vast literature which already has accumulated on it illustrates poignantly its tremendous importance, especially as it concerns statistical documentation in our time. Other facets, as for example, the cancerogenic effect of radiation on the non-protected skin or the development of bone sarcoma due to internal over-irradiation by absorbed radioactive substances in the watch dial painters, have found their positive interpretation in the past and resulted in the introduction of proper measures to prevent them. Still other facets, such as the study of less frequent specific conditions, like the malignant neoplasms of the thyroid and thymus; a careful appraisal of the reproductive history with the possible first generation or later congenital anomalies; and the proper interpretation of the much debated genetic heritage, are of immeasurable importance to the future and undoubtedly will need accurate scientific documentation beyond our unforeseeable time.

The American College of Radiology, fully realizing the implications of these problems and their impact on the welfare of mankind, has now initiated a long range study, conceivably extending into several generations, in which the radiologists, who have always been in the vanguard of pioneering and increasingly fostering protection against radiation hazards, will play the major role.⁷

This study, in the form of a Registry, is sponsored by the National Academy of Sciences-National Research Council and will be supervised by a specially selected

committee composed of members from the Council, the American College of Radiology, the College of the American Pathologists and the epidemiologists in charge of processing the data. It is extremely fortunate that the pathologists, who have always been of immeasurable aid in appraising the manifold radiation reactions produced and in guiding the radiologists to establish accurate dosage levels, have now been chosen to act as a "control" group in the study of the effects of various amounts of radiation on radiologists and in particular the effects of minimal exposure over a long period of time.

Recently, the American College of Radiology has sent to all members of the College a questionnaire form, which will serve as the basic document of the Registry. The strictest safeguards are being maintained and, to insure that the answers given will remain confidential, a code number is assigned to each participant so that the name need not appear on the questionnaire. The completed forms will be filed under lock and key in the office of the College.

A similar questionnaire is being sent to all members of the College of the American Pathologists.

The data of the questionnaires will be transferred to anonymous number IBM cards which then will be sent to Dr. Raymond Seltzer and Dr. Philip E. Sartwell of the School of Hygiene and Public Health, Johns Hopkins University, for processing. These cards cannot be released to anyone without the prior consent of the Colleges.

It is anticipated that the two sets of statistics—those for the radiologists and those for the pathologists—will yield in time extremely valuable comparative information which when placed in proper perspective will prove of unusual benefit to mankind. To obtain the highest degree of validity in this endeavour, the cooperation of every member of the two Colleges is earnestly solicited. The Executive Council of the American Roentgen Ray Society expresses support of the objectives of this study and the operating procedures established.

⁶ The Hazards to Man of Nuclear and Allied Radiations. A Second Report of the Medical Research Council, Dec., 1960, Cmnd. 1225, H. M. Stationery Office, Atlantic House, Holborn Viaduct, London, E.C.1, England (Price 7s. 0d net).

⁷ Radiation effects to be studied; new investigation seeks to find any effects, if any, of radiation on lives of radiologists and their children. *Your Radiologist*, 1961, 5, No. 2, 3-5.

NEWS ITEMS

TENTH INTERNATIONAL CONGRESS OF RADIOLOGY

The scientific program for the Tenth International Congress of Radiology which will be held in Montreal, Canada, August 26th-September 1st, 1962, will include thirty symposia and thirty general sessions arranged in sequence developing discussions of the general subject matter which was announced in the Preliminary Program issued in June 1961.

The titles for these symposia will be:

Diagnostic Radiology: Selective angiography (a) abdominal aorta, (b) coronary circulation, (c) cerebral circulation; renal disease including associated systemic changes; cineradiography; pediatric radiology; neuroradiology.

Therapeutic Radiology: Advances in knowledge of radiation effects on tissues of vital viscera in humans; clinical cancer therapy; clinical treatment planning; interstitial and intracavitary radiation therapy; clinical results of high energy radiation therapy; metabolized radioisotopes in therapy.

Radiation Physics: Concepts, quantities and units for radiation dosimetry; physical concepts in dosimetry; dosimetric methods; whole body counting and scanning.

Radiation Biology: New knowledge of the cell and its functions as derived by autoradiography; experimental studies of total body irradiation, marrow transplantation; toxicity and dose distribution of internal emitters and chemical protection against radiation.

Combined Symposia: Effects of radiation at the cellular and sub-cellular levels; clinical application of radiobiology at cellular and sub-cellular levels; high energy external beam therapy; total body irradiation and marrow transplantation at the clinical level; localization by isotope methods; external localization by radioisotope scanning; image amplification; dose in

diagnostic procedures; genetic and somatic implications of radiation and radiation protection.

These will include a number of joint programs devoted to special topics in which two or more of the general fields of diagnosis, treatment, physics and biology have interests in common.

Simultaneous translation in the four official languages will be provided for the symposia, which are being especially planned to cover developments during the last three years.

The papers proffered for the general sessions will be selected insofar as possible to form groups of common or related interest.

Radiologists, radiation physicists and radiobiologists, who intend to attend the Congress and especially those who wish to proffer scientific papers, scientific exhibits and scientific cine-films, are urged to complete the enrolment forms and other documents pertinent to such scientific communications at the earliest possible date.

Although the Congress Secretariat has attempted to reach all medical radiologists, radiation physicists and radiobiologists as well as other interested scientists who are known to various scientific societies around the world and has issued over 17,000 copies of the Preliminary Program, individuals who wish to attend and particularly those who desire to proffer such material but who have not received a Preliminary Program with the appropriate forms are invited to write to the Secretary-General, Tenth International Congress of Radiology, 1555 Summerhill Avenue, Suite 204, Montreal 25, Canada.

NEW OFFICERS OF THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

At the Forty-seventh Annual Meeting of the Radiological Society of North America held November 26-December 1, 1961, at Palmer House, Chicago, Illinois, the follow-

ing officers were elected: *President*—Charles M. Gray, M.D., Tampa, Florida; *President-Elect*—Ivan J. Miller, M.D., San Francisco, California; *First Vice President*—John A. Evans, M.D., New York, N. Y.; *Second Vice President*—Maurice M. Haskell, M.D., Long Beach, California; *Third Vice President*—Lester D. Shook, M.D., Fargo, North Dakota; *Secretary*—Maurice D. Frazer, M.D., Lincoln, Nebraska; *Treasurer*—Dwight V. Needham, M.D., Syracuse, New York; and *Historian*—Howard P. Doub, M.D., Detroit, Michigan. Dr. Robert P. Barden, Philadelphia, is the new *Chairman of the Board of Directors*.

The Gold Medal of the Society was awarded to Dr. L. Henry Garland of San Francisco, California. Dr. Elis Berven of Stockholm, Sweden, and Dr. Gioacchino Failla (recently deceased) were elected to honorary membership.

The Forty-eighth Annual Meeting will be held at Palmer House, Chicago, Illinois, November 25–30, 1962.

COURSE IN DIAGNOSTIC RADIOLOGY AT UNIVERSITY OF CALIFORNIA SAN FRANCISCO MEDICAL CENTER

A five-day conference on "Diagnostic Radiology" will be held at the University of California San Francisco Medical Center, March 14–16, 1962.

The conference, presented by Continuing Education in Medicine, University of California Extension, is planned primarily for practicing radiologists. Discussion subjects are arranged so that each day is devoted to one or two major subdivisions in the field, allowing physicians to attend lectures and panels of greatest interest to them.

Dr. Ulf G. Rudhe, professor of radiology, Tjanste, Karolinska Sjukhuset, Stockholm, Sweden, will be a guest faculty member. Other visiting faculty, joining the staff of the U. C. School of Medicine, include J. Scott Dunbar, assistant professor of radiology, McGill University; Melvin M. Figley, professor of radiology, University of Washington School of Medicine; Harold

C. Jacobson, professor of radiology, Emory University; Louis Lichtenstein, clinical professor of pathology and chief of anatomic pathology, Veterans Administration Hospital, San Francisco; and Harry Z. Mellins, professor of radiology and chairman of the department, State University of New York.

Further information and application for enrolment may be obtained from Continuing Education in Medicine, University of California School of Medicine, Third and Parnassus, San Francisco, California.

COURSE IN RADIOLOGY AND RADIOACTIVE ISOTOPES AT THE UNIVERSITY OF KANSAS MEDICAL CENTER

A three-day postgraduate course in Radiology and Radioactive Isotopes will be given February 19, 20 and 21, 1962 at the University of Kansas Medical Center. The course is presented by the University of Kansas School of Medicine in cooperation with The Radiological Society of Greater Kansas City, The Kansas Medical Society, The Kansas State Board of Health, aided by grants from The Kansas Division, Inc., American Cancer Society and The Kansas Radiological Society.

An outstanding guest faculty, selected for their teaching as well as clinical abilities, has been assembled for this program. Recent advances in some of the newer developments of radiology will be discussed and a review of some of the basic problems confronting the radiologist and the internist will be presented.

For further information, please write to William D. Nelligan, Executive Director, Department of Postgraduate Medical Education, University of Kansas School of Medicine, Kansas City 3, Kansas.

SYMPOSIUM OF TECHNOLOGICAL NEEDS FOR REDUCTION OF PATIENT EXPOSURE FROM DIAGNOSTIC RADIOLOGY

The Research Branch, Division of Radiological Health, United States Public Health Service is sponsoring a symposium en-

titled, "Technological Needs for Reduction of Patient Exposure from Diagnostic Radiology." The purpose of this meeting is to evaluate the status of laboratory research as it applies to this subject. Approximately fifteen papers will be given which will summarize the state of the art and point out future areas for investigation. The four main categories which will be covered are human and phantom dosimeters, radiographic equipment, fluoroscopic and intensifier equipment, and

radiographic grids, screens, and films. Drs. H. Wycoff, C. Braestrup, R. H. Morgan, and E. W. Webster will act as moderators for these sessions.

The dates of this meeting are March 5 and 6, 1962. The place is the main auditorium of the Health, Education, and Welfare Building, Washington, D. C.

For information and tickets contact: M. L. Janower, M.D., Division of Radiological Health, HEW South Penthouse, Washington 25, D. C.

It is with deep regret that we announce the death of Dr. Gioacchino Failla, distinguished scientist and a member of the American Radium Society and associate member of the American Roentgen Ray Society. Dr. Failla was killed in an automobile accident in Chicago on December 18, 1961.



BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

THE YEAR BOOK OF RADIOLOGY (1960-1961 Year Book Series). Edited by John Floyd Holt, M.D., Professor, Department of Radiology, University of Michigan; Walter M. Whitehouse, M.D., Associate Professor, Department of Radiology, University of Michigan; Harold W. Jacox, M.D., Professor of Radiology, College of Physicians and Surgeons, Columbia University; Chief, Radiation Therapy Division, Radiologic Service, Presbyterian Hospital, New York City; and Morton M. Kligerman, M.D., Professor of Radiology and Chairman of the Department of Radiology, Yale University School of Medicine; Director of Radiology, Grace-New Haven Community Hospital. Cloth. Price, \$11.00. Pp. 441, with 305 illustrations. Year Book Publishers, Inc., 200 East Illinois Street, Chicago, Ill., 1961.

The current Year Book of Radiology, 1960-1961 series, perpetuates this fine annual edition to the busy radiologist's library. Its value is unquestioned by those who own copies of previous series. Between the familiar blue and red cover bindings the authors have painstakingly packed condensations of hundreds of the most significant articles pertaining to this specialty from the world medical literature of the past year. Those who would keep abreast of the innovations and latest trends in their chosen field will find this book hard to put down once the first few pages have been perused.

The authors are unexcelled in their ability to produce readable condensations which retain sufficient data, including statistics, graphs, tables, and roentgenographic reproductions where indicated. One seldom needs to refer to original articles. Sage editorial comments are freely employed with frequent references to non-abstracted monographs and to previous Year Book editions.

The usual balance between diagnostic and therapeutic subjects has been maintained. Drs. Holt and Whitehouse have reviewed both foreign and domestic specialty journals obtaining articles of value which few radiologists have encountered. Although no startling innovations in technical equipment have appeared, new appli-

cations have made progress rapid. New arteriographic and venographic techniques are but one example. Cine techniques have been extended to all portions of the gastrointestinal tract.

Drs. Jacox and Kligerman have surveyed the significant foreign and domestic reports relating to radiation therapy, radiobiology, physics, hazards, and injuries. They have concentrated on reports dealing with very large series of cases. Even the experimental material reviewed should be of general interest to the average radiologist.

ARCH H. HALL, M.D.

NEURORADIOLOGY WORKSHOP. Vol. I. Scalp, Skull and Meninges. By Leo M. Davidoff, M.D., Active Consultant Neurosurgeon, Montefiore Hospital; Professor and Chairman, Department of Neurosurgery, Albert Einstein College of Medicine, Yeshiva University, New York; Harold G. Jacobson, M.D., Chief, Division of Diagnostic Radiology, Montefiore Hospital; Professor of Clinical Radiology, New York University School of Medicine, New York; and Harry M. Zimmerman, M.D., Chief, Division of Laboratories, Montefiore Hospital; Professor of Pathology, College of Physicians and Surgeons, Columbia University, New York. Cloth. Price, \$16.50. Pp. 256, with many illustrations. Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, N. Y., 1961.

This book consists of a series of edited, expanded and re-arranged weekly conferences held in the Department of Radiology of the Montefiore Hospital, New York City. The participants are mainly from the staffs of the Departments of Neurology, Neurosurgery, Radiology and Pathology. The clinical features of each case are first presented, then the radiological findings. Discussion of the findings by senior members of the various departments follows and a provisional diagnosis with differential diagnosis is offered by each. Then the findings at operation and the pathologist's diagnosis are disclosed. The presentation ends with a short discussion covering various features of the lesion under consideration.

This volume, Volume 1, is confined to tumors of the scalp and skull. It describes 42 cases of which 38 are meningiomas. It contains much practical information. Since it is given in discursive fashion, it requires careful reading to extract the information. It also presupposes a moderate knowledge of neurology, radiology and pathology and therefore cannot be recommended to medical students. Residents in neurology, neurosurgery and radiology could gain from it but it does not replace standard textbooks on those subjects. In several cases, only a curt statement of the pathological diagnosis is given. A photomicrograph or a brief description of the pathological findings in each case would be valuable.

In the Preface, some criticism of the classical "vertical" and "horizontal" presentations of standard textbooks is made. It is suggested that the conference type of approach such as used in this book overcomes this criticism. This reviewer has not been impressed by conference type of teaching unless the students already have a thorough vertical and horizontal basis of clinical, radiological and pathological facts.

DONALD L. McRAE, M.D.

THE PATHOLOGY OF IONIZING RADIATION. By Shields Warren, M.D., Sc.D., LL.D., Professor of Pathology, Harvard Medical School at the New England Deaconess Hospital; Pathologist, New England Deaconess and New England Baptist Hospitals, Boston, Mass. Cloth. Price, \$3.00. Pp. 42, with 17 illustrations. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1961.

This brief monograph is based on two of Dr. Warren's lectures to State Pathological Societies and as such is not an attempt to cover the effects of irradiation upon the body by a systematic organ by organ description. As it is presumed that readers know something already of the anatomic pathology in various organs, the emphasis is more general and is based largely on a discussion of the acute radiation syndrome. Following a brief résumé of the historical aspects, the intracellular action of radiation is discussed, especially the effects on nucleoproteins. The action of absorbed radioisotopes on tissues is covered superficially and is followed by a more complete discussion of the

action of radiation on tumors, consideration being given to the various factors rendering a tumor resistant or sensitive. A few pages are devoted to the carcinogenic effect of irradiation and the monograph concludes with mention of the effects of radioactive fall-out.

The book is not recommended for the medical student or resident seeking organ by organ information on the pathology of irradiation but it does provide a good review of the current status of knowledge. The author is an authority in the field and the book is very readable. The bibliography provides those interested with the means of furthering their knowledge.

A. R. W. CLIMIE, M.D.

BOOKS RECEIVED

ANATOMY OF THE CORONARY ARTERIES. By Thomas N. James, M.D., F.A.C.P., Chairman, Section on Cardiovascular Research, Henry Ford Hospital, Detroit, Michigan. Cloth. Price, \$18.00. Pp. 211, with 136 illustrations of which 42 are in color. Paul B. Hoeber, Inc., 49 East 33rd Street, New York 16, N. Y., 1961.

HISTOPATHOLOGY OF THE SKIN. Third edition. By Walter F. Lever, M.D., Professor of Dermatology and Chairman of the Department, Tufts University; Lecturer on Dermatology, Harvard University; Director, Dermatology Service, Boston City Hospital; Physician-in-Chief, Dermatology Clinic, Boston Dispensary; Physician (Dermatology), Boston Floating Hospital for Children; Member of the Board of Consultation, Massachusetts General Hospital; Consultant in Dermatology, Peter Bent Brigham Hospital and Robert Breck Brigham Hospital, Boston, Mass. Cloth. Price, \$16.50. Pp. 653, with 320 illustrations of which 8 are in color. J. B. Lippincott Company, East Washington Square, Philadelphia 5, Pa., 1961.

MONOGRAPHS OF THE SOCIETY FOR RESEARCH IN CHILD DEVELOPMENT. STUDIES OF ILLNESSES OF CHILDREN FOLLOWED FROM BIRTH TO EIGHTEEN YEARS. By Isabelle Valadian, Harold C. Stuart, and Robert B. Reed, Harvard University School of Public Health, 55 Shattuck Street, Boston 15, Mass. Paper. Price, \$3.25. Pp. 125, with many illustrations and tables. Child Development Publications, Purdue University, Lafayette, Indiana, Vol. 18. 1961.

NUKLEARMEDIZIN IN DER KLINIK. By Lee E. Farr, Brookhaven; H. W. Knipping, Cologne; and William H. Lewis, New York. Cloth. Pp. 486, with many illustrations. Westdeutscher Verlag, Cologne, Germany, 1961.

ABSTRACTS OF RADIOLOGICAL LITERATURE

INDEX TO ABSTRACTS

ROENTGEN DIAGNOSIS

HEAD

- LUDOVICO, N.: Roentgenologic examination of the foramen jugulare; on a new technique and the use of oblique thick layer laminagraphy..... 406
- MONES, R. J., CHRISTOFF, N., and BENDER, M. B.: Posterior cerebral artery occlusion; a clinical and angiographic study..... 406

NECK AND CHEST

- DISTELMAIER, A. *et al.*: A new contrast medium for bronchography: broncho-abrodil..... 406
- KÖSTER, E., and MEYER, H. J.: Bronchography with a new contrast medium..... 406
- JONES, H. E., and HOWELLS, C. H. L.: Pulmonary agenesis..... 407
- SCHWARTZ, A., and BORMAN, J. B.: Contusion of the lung in childhood..... 407
- BEYER, A., RICHTER, K., and ERIBO, O.: Two cases of Hamman-Rich-syndrome with recurrent spontaneous pneumothorax..... 407
- CANOSSI, C., VENDRAME, L., and AMICI, F.: Studies on localized pulmonary lesions of Besnier-Boeck-Schaumann disease..... 408
- MOSETITSCH, W.: Amyloid tumors of the lungs..... 408
- CAMERON, D. G. *et al.*: Idiopathic mediastinal and retroperitoneal fibrosis..... 409
- GOLDSTEIN, M., and DUMONT, A.: Results and interpretations of phlebographic studies of the mediastinum and thorax..... 409
- TORI, G., and GARUSI, G. F.: Angiocardiographic diagnosis of Ebstein's anomaly of the tricuspid valve; presentation of three

cases..... 409

- AYAS, E., VISPO, A., and DEMARCHI, R.: Esophagogastric fibroleiomyomas..... 410

RADIATION THERAPY

- WACHSMANN, F.: From radium contact therapy through contact radiation to soft radiation and therapy with beta rays or fast electrons. 410
- LÜDICKE, K.: The radiographic appearance of radiation changes in the ilium and sacrum. 411
- RUBIN, P., and PRABHASAWAT, D.: Characteristic bone lesions in post-irradiated carcinoma of the cervix..... 411

RADIOISOTOPES

- ROSENBERG, I. N., and CHALFEN, M. H.: Effect of thyrotropin upon release of iodide from human and rat thyroid..... 411
- FRETHEM, A. A., ALBERT, A., and KEATING, F. R., JR.: Iodine metabolism in surviving thyroid slices from patients with exophthalmic goiter..... 412
- McKENZIE, J. M.: Studies on the thyroid activator of hyperthyroidism..... 412
- BUCHANAN, W. W. *et al.*: Iodine metabolism in Hashimoto's thyroiditis..... 412
- LEBOEUF, G. *et al.*: Immunologic and thyroid function studies in euthyroid children with goiter..... 413
- BONNET, J. D. *et al.*: A simple direct method for determining radioactivity in feces..... 413
- BARLOW, C. F. *et al.*: Extracellular brain space measured by S³⁵ sulfate..... 414
- FREY, E., MATTER, H., and PESTALOZZI, D.: Transnasal implantation of yttrium 90 rods in a largely suprasellar, hypophyseal tumor. 414



ROENTGEN DIAGNOSIS

HEAD

LUDOVICO, N. L'indagine radiologica dei canali lacerti posteriori; utilità di una nuova incidenza e dell'impiego della stratigrafia obliqua a strato spesso. (Roentgenologic examination of the foramen jugulare; on a new technique and the use of oblique thick layer laminagraphy.) *Radiol. med.*, Aug., 1961, 47, 700-710. (Address: Dott. Prof. Nicola Ludovico, Via Molinari 3, Brescia, Italy.)

The procedure proposed by the author for the roentgenographic examination of the foramen jugulare is limited to the use of the craniograph. The patient lies supine, the head fully extended. The tube is angled with a primary tilting of 27° cranially and then with another primary tilting 22° toward the opposite side to be examined.

For laminagraphic studies of the foramen jugulare the author recommends the technique of oblique thick layer laminagrams. The patient is in the same position with the head fully tilted backward. The exposure takes place only during the initial stage of the movement of the laminagraph.—*A. F. Govoni, M.D.*

MONES, R. J., CHRISTOFF, N., and BENDER, M. B. Posterior cerebral artery occlusion; a clinical and angiographic study. *A.M.A. Arch. Neurol.*, July, 1961, 5, 68-76. (From: The Department of Neurology, The Mount Sinai Hospital, New York, N. Y.)

An analysis of 106 consecutive vertebral angiograms was made in an effort to determine the clinical significance of non-filling of one or both posterior cerebral arteries. Previous reports have called attention to the variations in the posterior circulation. In one series the basilar posterior cerebral artery connection was absent on one side in 1.5 per cent of cases, but bilateral absence of the basilar artery connection to posterior cerebral arteries was not seen.

The published reports have not correlated absence of filling of the posterior cerebral artery with the clinical symptoms, and in the present study a particular attempt was made to do this.

When there is a lack of filling of one posterior cerebral artery on vertebral angiography and the patient has contralateral homonymous hemianopsia, carotid studies are necessary for complete evaluation of the vascular system. It is suggested that failure of one posterior cerebral artery to fill on vertebral and ipsilateral carotid angiography is abnormal and indicates occlusive disease of the non-filled posterior cerebral artery. Non-filling of both posterior cerebral arteries in vertebral angiography is abnormal. All six patients with non-filling of these arteries had

clinical evidence of brain stem and occipital lobe disease.

It is concluded, therefore, that vertebral angiography is a valuable method of studying occlusive vascular disease of the posterior circulation, but only when non-filling is verified by carotid artery injection.—*Lois Cowan Collins, M.D.*

NECK AND CHEST

DISTELMAIER, A., GLOXHUBER, CH., GREMMEL, H., HECHT, G., SCHOLTAN, W., VIETEN, H., and WILLMANN, K. H. Ein neues Kontrastmittel für die Bronchographie: Broncho-Abrodil. (A new contrast medium for bronchography: Broncho-Abrodil.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Aug., 1961, 95, 155-165. (Address: Prof. Dr. H. Vieten, u. a., Institut und Klinik für Med. Strahlenkunde der Med. Akademie, Moorenstr. 5, Düsseldorf, Germany.)

The newly developed contrast material, Broncho-Abrodil, is a suspension of Abrodil with a low solubility. It is not as hypertonic as the previously used water-soluble contrast substances, and therefore less irritating. Its solubility is great enough to be absorbed from the bronchial tree in 2 or 3 days. No substances have been added to control the viscosity. Its viscosity increases with rising temperature. The filling of capillary spaces and alveoli is avoided. General and local tolerance is excellent. Side effects in animals and humans are practically absent. Practical points in the use of this new contrast material for bronchography are added.—*Hans W. Hefke, M.D.*

KÖSTER, E., and MEYER, H. J. Bronchographie mit einem neuartigen Kontrastmittel. (Bronchography with a new contrast medium.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Aug., 1961, 95, 166-172. (Address: Oberarzt Dr. med. E. Köster, Fachklinik der LVA Oldenburg-Bremen, Germany.)

Pure iodized oils have the best affinity to the mucosa of the bronchial tree and give good contrast. But because of their fluidity they fill the alveoli and may cause complications arising from it. Other contrast media have often undesirable side effects, such as increased bronchial irritation by water soluble media.

A new contrast preparation called Bayer 1238 or Broncho-Abrodil was used by the authors in 123 cases of bronchography. Its main difference from older media is the fact that its viscosity increases from room temperature to body temperature so much that it does not enter the alveolar spaces. The bronchography itself appears less irritating than with

previous media. In normal lungs the contrast substance disappeared completely in 2-24 hours; in abnormal lungs it took, at times, 2-4 days before no evidence of contrast material was seen on the check films.

The authors recommend this new bronchographic medium.—*Hans W. Hefke, M.D.*

JONES, H. E., and HOWELLS, C. H. L. Pulmonary agenesis. *Brit. M. J.*, Nov., 1961, 2, 1187-1189. (From: The Royal Hospital, Wolverhampton, England.)

Three cases of complete absence of one lung are reported with a fourth in which the middle and lower lobes were absent. Two of those with total agenesis died before one year of age and one is cyanosed and dyspneic on exertion at the age of two years. The child with partial agenesis is $4\frac{1}{2}$ and appears to be doing quite well.

Pulmonary agenesis is frequently accompanied by other anomalies which are the cause of the child's demise. Occasionally patients reach an advanced age.

The characteristic roentgen appearance is one of shift of the heart into the affected hemithorax in which no lung is visible. In complete agenesis bronchography reveals no bronchus leading to the abnormal side.

The differential diagnosis in infancy includes diaphragmatic hernia, pneumothorax (especially associated with *Staphylococcus pneumoniae*), lobar emphysema and dextrocardia.—*David Morse, M.D.*

SCHWARTZ, A., and BORMAN, J. B. Contusion of the lung in childhood. *Arch. Dis. Childhood*, Oct., 1961, 36, 557-561. (From: The Departments of Diagnostic Radiology and Thoracic Surgery, Hadassah University, Jerusalem, Israel.)

Children involved in a rapid deceleration type of accident frequently have blunt trauma to the chest without rib fracture. Pain in the chest is, therefore, minimal and the attention of the clinician is directed toward the other injuries. Pulmonary contusion is not infrequent in these cases. This may be present without respiratory symptoms.

The roentgenogram often reveals fuzzy opacities of varying size and density with irregular borders. Pneumothorax, hemothorax or both may be present. Pneumomediastinum, hemomediastinum and subcutaneous emphysema are not infrequent. The underlying pathology of this roentgenographic abnormality may be interstitial hematoma, acute localized edema, patchy confluent atelectasis and intra-alveolar hemorrhage. These contusions do not require surgical intervention. Those with lung contusion alone should receive prophylactic antibiotics. They should be kept under hospital surveillance until the lungs are clear. Round or ring shadows have been

reported as resulting and these may persist for three months.—*David Morse, M.D.*

BEYER, A., RICHTER, K., and ERIBO, O. Zwei Verlaufsbeobachtungen eines Hamman-Rich-Syndromes mit rezidivierendem Spontanpneumothorax. (Two cases of Hamman-Rich syndrome with recurrent spontaneous pneumothorax.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, May, 1961, 94, 568-579. (From: Röntgenabteilungen der I. Medizinischen Universitätsklinik und Poliklinik der Charité, Berlin, Germany.)

The Hamman-Rich syndrome is a rare diffuse interstitial pulmonary fibrosis. It is usually fatal within a few months or years. In the benign form, however, a nine year survival has been observed.

Clinically, the progressive fibrosis results in respiratory insufficiency with right heart failure. Histologic study of needle biopsy material reveals intra-alveolar proliferation of connective tissue. Roentgenologically, there is a reticulated honeycombed fibrotic pattern with interspersed miliary and small nodular densities, leading to large confluent formations. The lesions are symmetric and are located in the lower and middle lung fields, rarely extending upward to the upper lobes. Occasionally, hilar lymphadenopathy occurs. Associated spontaneous pneumothorax has only been observed twice. Two cases are herewith reported with development of recurrent pneumothorax.

The first patient was a male, aged fifty eight, with a six year history of progressive dyspnea. Roentgenologic study demonstrated reticulated fibrosis mostly of upper lobes with small nodulation and progressive shrinking. There was compensatory emphysema of the lower lobes. Recurrent spontaneous pneumothorax developed bilaterally. Functional studies revealed decrease of the total and vital capacity. There was a rapid downhill course in spite of steroid therapy. The patient finally died with the clinical course of right heart failure. Postmortem examination showed characteristic diffuse interstitial pulmonary fibrosis, pleural adhesions, and cor pulmonale.

The second patient was a male, aged thirty eight, with a right lower lobe pneumonia which developed into the Hamman-Rich syndrome. Roentgenologic study revealed reticulated fibrotic changes with honeycombing in both upper and middle lung fields and hilar lymphadenopathy. Steroid therapy was without benefit. After two years a spontaneous pneumothorax developed over the right apex and four months later over the entire left lung. Following re-expansion of the lungs confluent small nodular lesions were observed within the fibrotic strands. The hilar lymphadenopathy remained stationary, but the fibrotic lesions were progressive. The total and vital

capacity was moderately diminished, and there was progressive dyspnea.

The characteristic lesions usually are perihilar and in the middle and lower lung fields. Thus, localization in the upper lobes in the two cases is unusual, thereby simulating tuberculosis, Hodgkin's disease and silicosis. The clinical, roentgenologic, and pathophysiologic pattern is fairly typical so that a correct diagnosis is possible in most instances.

The following conditions have to be considered in the differential diagnosis: (1) pulmonary fibrosis with known etiology (pneumoconiosis and sarcoidosis, leading to hilar lymphadenopathy); (2) pulmonary fibrosis with unknown etiology; (3) systemic disease with associated pulmonary fibrosis (scleroderma, systemic progressive sclerosis and other collagenous disorders); and (4) congenital and acquired honeycombing of lungs (causing respiratory obstruction in contrast to free air passages in the Hamman-Rich syndrome).—*Ernest Kraft, M.D.*

CANOSSI, C., VENDRAME, L., and AMICI, F.
Contributo allo studio delle localizzazioni polmonari del morbo di Besnier-Boeck-Schaumann. (Studies on localized pulmonary lesions of Besnier-Boeck-Schaumann disease.) *Ann. radiol. diag.*, 1961, 34, 132-159. (From: Istituto di Radiologia dell'Università di Modena, Modena, Italy.)

The authors review the historic contribution of various investigators to this entity with the first description by Besnier in 1889. Although this disease involves the reticuloendothelial system of every organ of the body, the lungs are most often affected.

The etiology, which remains unknown, is discussed with the theoretic and investigative hypotheses which have been proposed.

The symptoms in this disease are vague and vary with the organs involved. The only symptoms may be asthenia and recurrent upper respiratory infections. There may be an unexplained loss of weight, fatigue, and mild degree of dyspnea. Laboratory studies may show only an increase in sedimentation rate—with yhyperglobulinemia and hypercalcemia. The disease runs a benign course and the patient may survive many years with the minimum of symptoms and morbidity.

The histopathologic aspects are discussed with the differential diagnosis of tuberculous, fungous, and other granulomatous diseases.

The authors report 8 cases with hilar and pulmonary disease. Various forms of treatment were used, such as steroids, PAS, ACTH, etc., including radiation therapy with doses of 1,500 to 2,400 r to the mediastinum. Of these 8 patients, 5 received radiation therapy either alone or in conjunction with other medication; 3 of them improved and 2 remained unimproved. Regardless of the treatment adminis-

tered to the 8 patients, the results were not uniform and therefore difficult to evaluate.

The diagnosis in these cases is still made by roentgenographic studies and microscopic examination of the lymph nodes.

The only criticism that the reviewer would like to offer is the high radiation dose (1,500-2,400 r) given for a benign disease and especially to a group of patients in the twenty-five to thirty-five year age group. Otherwise this is an excellent article on the subject.—*Peter E. Russo, M.D.*

MOSETITSCH, W. Amyloid "Tumoren" der Lungen. (Amyloid tumors of the lungs.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, May, 1961, 94, 579-587. (Address: Dr. W. Moseitsch, Röntgeninst. der Thoraxklinik, Karolinska Sjukhuset, Stockholm, Sweden.)

There are two types of amyloidosis: the typical, which is secondary to chronic inflammatory processes, malignant tumors and myelomatosis, and the atypical, which is idiopathic without recognizable underlying disease. Both types are usually characterized by a diffuse amyloid infiltration of various organs. In exceptional cases, however, the amyloid material is localized, thereby simulating neoplastic formations. Three cases are reported and illustrated in which the trachea, bronchi and lung periphery were the sites of idiopathic amyloid tumors.

The first patient was a male, aged sixty who was hospitalized for pneumonia. Roentgenograms of the chest demonstrated a massive density in the periphery of the right upper lobe and streaky formations leading from this area to the right hilus. The latter was enlarged. Bronchoscopy revealed irregular thickening of the right upper lobe bronchus. Needle biopsy of this area disclosed amyloid tumor.

The second patient was a male, aged thirty-nine, with a five year history of progressive dyspnea. Roentgenograms of the chest showed irregular narrowing of the lower two thirds of the trachea with tumorous masses protruding into its lumen. Bronchoscopy disclosed neoplastic involvement of the right lateral wall of the trachea, extending downward to the right upper lobe bronchus. Needle biopsy material proved to be amyloid substance.

The third patient was a female, aged thirty-seven, with a respiratory infection. Roentgenograms of the chest showed lobulated masses above the right base and in the left middle lung field. Faint calcific deposits were noted in some of the lesions. Bronchography and arteriography failed to reveal any specific findings. Histologic study of biopsy material from the bronchial wall disclosed amyloid formations.

The tumorous lesions are characterized by a slow growth, lacking characteristic appearance; therefore, exploratory thoracotomy or needle biopsy may become necessary for diagnostic purposes. In most

instances, however, bronchoscopic biopsy may suffice.

The pulmonary lesions can simulate tuberculosis, sarcoidosis, histoplasmosis and lipoidosis. A malignant lesion can be excluded when calcific deposits are found in the masses.—*Ernest Kraft, M.D.*

CAMERON, DOUGLAS G., ING, S. T., BOYLE, M., and MATHEWS, W. H. Idiopathic mediastinal and retroperitoneal fibrosis. *Canad. M.A.J.*, July, 1961, 85, 227-232. (From: Department of Medicine, The Montreal General Hospital; Department of Medicine, Queen Mary Veterans Hospital; and Department of Pathology, The Montreal General Hospital, Montreal, Quebec, Canada.)

Idiopathic mediastinal fibrosis is a rare disorder, but cases have been reported sporadically since the first case was described by John Hunter in 1757. Reports have been increasing in frequency in recent years as have those of the retroperitoneal counterpart, which was first described in 1948. To date 65 cases of retroperitoneal fibrosis have been reported.

Three additional cases are described, two with idiopathic retroperitoneal fibrosis, and one with combined mediastinal and retroperitoneal fibrosis.

The pathology of the two conditions is strikingly similar and consists of hard, fixed white fibrous tissue in the mediastinum and/or the retroperitoneal area, causing constriction of the great vessels, and in the latter area, of the ureters. The process is usually self-limited, but may be complicated by thrombosis. In the retroperitoneal area the ureteral constriction may lead to fatal renal complications if the ureteral obstruction is not surgically relieved.

The etiology remains obscure. Corticosteroid therapy or irradiation and antibiotics have been used, but since the majority of cases is self-limited, results are difficult to assess. Undoubtedly early diagnosis and surgical release of the strangled ureters may be life-saving.

The three cases reported support the view that the two conditions are variants of a single disease process.—*Lois Cowan Collins, M.D.*

GOLDSTEIN, M., and DUMONT, A. Résultats et interprétations des explorations phlébographiques du médiastin et du thorax. (Results and interpretations of phlebographic studies of the mediastinum and thorax.) *Acta chir. belg.*, Feb., 1961, No. 2, 168-189. (From: Département de Chirurgie thoracique, Département de Chirurgie vasculaire, and Service de Chirurgie générale, Hôpital universitaire Saint-Pierre, Bruxelles, Belgium.)

In a previous report (*Acta chir. belg.*, Suppl. II, pp. 110-131, June 1960) the authors have described their techniques for mediastinal and azygos phlebog-

raphy. They have now examined 89 cases, including neoplasms of the bronchi, mediastinum, thyroid, esophagus and breast; also pulmonary tuberculosis and the superior vena cava syndrome. The methods are highly useful in demonstrating deformities of the venous trunks, and therefore for determining operability in neoplasms and particularly in the superior vena cava syndrome. If in the future venous grafts are used more often in the latter condition venography will be indispensable in indicating the length of segments to be replaced.

The authors consider their method of azygography, in which 10 cc. of opaque medium is injected into a rib, to be simpler than the Marcozzi method of introducing contrast material via the vertebral system.—*Frank A. Riebel, M.D.*

TORI, G., and GARUSI, G. F. La diagnosi angiocardigrafica nella anomalia tricuspidaica tipo Ebstein; presentazione di tre osservazioni personali. (Angiocardiographic diagnosis of Ebstein's anomaly of the tricuspid valve; presentation of three cases.) *Radiol. med.*, Aug., 1961, 47, 673-688. (Address: Dott. Prof. Giulio Tori, Via Mezzofanti 89, Bologna, Italy.)

In the past ten years about 200 cases of Ebstein's anomaly of the tricuspid valve have been reported in the world literature.

The symptomatology of this anomaly shows a great variability. The most frequent symptoms are: dyspnea, extrasystolic arrhythmia, paroxysmic tachycardia and precordial pain. Cyanosis, mild or severe, is present in about 60 per cent of the cases. One feature of the cyanosis has been found to be quite constant. Present in the neonatal period, slowly regresses to reappear in early adolescence of adult life. Sotgiu *et al.* (La Malattia di Ebstein. Cappelli Ed., Bologna, 1959), have found also: (1) that the severity of the cyanosis is not related to the functional capacity of the heart, and (2) that the cyanosis gives to the face of the patient a rather typical small mask appearance.

Clinically there are systolic and diastolic murmurs, although in many cases only systolic (over the precordium), and abnormal rhythms. Symptoms related to a right heart insufficiency are rather frequent.

The most typical roentgen finding is marked enlargement of the heart which assumes a rather globular appearance. In cases in which there is dilatation of the right ventricular outflow tract the middle arch of the left border of the heart shows a characteristic bulging directed toward the left chest wall, giving the heart a box-like appearance, which is generally thought to be typical of Ebstein's anomaly. The borders of the heart show decreased pulsations except in the infundibulum of the right ventricle. The pulmonary artery is usually difficult to visualize and, when not hidden, shows regular pulsations. In

contrast with the severe enlargement of the heart is the decreased pulmonary vasculature, seldom normal. The hilar shadows are usually small. The left atrium is never enlarged and the size of the left ventricle is within normal limits. One must, however, remember that there are cases in which the cardiac shadow is essentially normal.

Angiocardiography in Ebstein's anomaly is recommended by some authors and objected to by others. The main criticism is based on the possibility of severe arrhythmias secondary to a sudden overflowing of the right chambers of the heart.

The authors have found that angiocardiography by the usual intravenous injection of the contrast medium is preferable to the direct visualization of the right heart following cardiac catheterization. They have adopted that procedure in 3 cases which are presented in detail.

The most common angiocardiographic findings were: (1) Marked enlargement of the right atrium with considerable dilatation of the auricular appendage. (2) The right atrium formed with the supra-valvular portion of the right ventricle a large atrio-ventricular chamber. The supraventricular portion showed minimal changes during the various cardiac phases. (3) The tricuspid valve was generally displaced to the left and quite high. (4) The infundibulum of the right ventricle was markedly dilated, appearing opacified even in the first angiogram and bulged outward, at the level of the superior half of the left border of the heart. In the lateral view the infundibulum formed, together with a dilated auricular appendage, the anterior border of the cardiac shadow. (5) Under the infundibulum, in the postero-anterior projection, in some cases it was possible to visualize the inferior or distal portion of the right ventricle which presented significant volumetric changes during the different stages of the cardiac contractions. This portion filled generally later than the great atrio-ventricular chamber and the infundibulum, and appeared therefore clearly outlined between them. (6) The pulmonary artery was almost completely hidden by the infundibulum of the right ventricle in the posteroanterior projection and in the left lateral projection also by the enlarged right auricular appendage. The main branches of the pulmonary artery were decreased in diameter. The transit of the contrast medium through the pulmonary bed appeared increased. The pulmonary veins were more easily identified. (7) An interatrial septal defect—right to left—was demonstrated in all cases by (a) early faint opacification, although not constant, of the left atrium; (b) by an early filling of the left ventricle and subsequently; (c) by early opacification of the aorta. The latter sign was the most constant and proved to be the one of greater diagnostic importance. (8) The contrast medium opacified for quite a while the right atrium and ventricle and the infundibulum. These were outlined by the contrast medium, although faintly, even in the angiocardi-

grams exposed at 10" to 12" from the injection of the contrast medium. The authors feel that this feature was highly typical and indicative of an Ebstein's anomaly of the tricuspid valve. (9) The left ventricle, but mainly the aorta, also remained opacified for quite some time. (10) In those cases in which the foramen ovale was not patent, other authors have found that the left ventricle and in particular the aorta did not show an early opacification, while all the other angiocardiographic findings were essentially similar to the ones observed by Tori and Garusi.

Concluding, the authors feel that angiocardiography is very useful in the diagnosis of Ebstein's anomaly of the tricuspid valve, due to a complex of roentgen features which together are quite pathognomonic.—*A. F. Govoni, M.D.*

AYAS, EDUARDO, VISPO, ALFREDO, and DEMARCHI, RAUL. Fibroleiomiomas esofagogastricos. (Esophagogastric fibroleiomyomas.) *Prensa méd. argent.*, Dec. 30, 1960, 47, 3405-3413. (Address: Pueyrredon 1493, Buenos Aires, Argentina.)

The most frequent site of leiomyomas was found to be the lower part of the esophagus, near the junction of the esophagus and stomach. These tumors are generally intramural. Although they are relatively rare, they can be diagnosed and surgically extirpated by a transthoracic approach.

Three cases of fibroleiomyoma of the esophagus are reported. One of these tumors situated in the middle third of the esophagus was asymptomatic. At operation, it was found to contain calcifications as the result of degeneration and mass hemorrhage into the tumor. The second tumor was situated at the lower extremity of the esophagus near the stomach and was associated with dysphagia. The third tumor was found at the junction of the stomach and esophagus and was the site of an esophagitis, also causing dysphagia.—*M. M. Friedman, M.D.*

RADIATION THERAPY

WACHSMANN, FELIX. Von der Radium-Kontaktbestrahlung über die Nahbestrahlung zur Weichstrahltherapie und zur Therapie mit Betastrahlen oder schnellen Elektronen. (From radium contact therapy through contact radiation to soft radiation and therapy with beta rays or fast electrons.) *Strahlentherapie*, Mar., 1961, 114, 446-453. (From Institut für Physikalische und Medizinische Strahlenkunde der Universität, Erlangen, Germany.)

The sharp drop in depth dose with radium contact therapy can be attained as well with soft radiation. Soft radiation avoids the disadvantage of contact therapy (Chaoul) of having to use many fields when a

large area is to be treated; further, the superficial dose is more homogeneous with soft rays when uneven surfaces are treated. Sharp drop of depth dose in treatment of large areas with soft radiation therapy is surpassed only by therapy with beta rays or fast electrons.—*Henry G. Moehring, M.D.*

LÜDICKE, KURT. Das Erscheinungsbild radiogener Veränderungen im Darmbein und Kreuzbein. (The radiographic appearance of radiation changes in the ilium and sacrum.) *Strahlentherapie*, Feb., 1961, 114, 286–295. (From: Universitäts-Geschwulstlinik der Charité, Berlin, Germany.)

In addition to the well known skeletal changes following irradiation of the pelvis (about the hip and in the pubis and ischium), both sclerotic and web-like osteolytic changes may occur in the iliac wings and the sacrum. These latter results remain relatively unknown because their clinical import is overshadowed by post-radiation changes about the hip.

Three patients retreated for residual pelvic tumors showed extensive skeletal damage; less severe changes were noted following primary radiation therapy of pelvic tumors. Every retreatment of residual pelvic tumor in patients who have had primary radiation therapy for carcinoma of the uterine cervix carries great risk of radiation osteonecrosis; the therapist, however, dare not let this risk prevent him from administering adequate radiation to such residual tumor.—*Henry G. Moehring, M.D.*

RUBIN, PHILIP, and PRABHASAWAT, DUSDEE. Characteristic bone lesions in post-irradiated carcinoma of the cervix. *Radiology*, May, 1961, 76, 703–717. (Address: Philip Rubin, 260 Crittenden Blvd., Rochester 20, N. Y.)

In a group of 259 cases of carcinoma of the cervix treated by irradiation at Strong Memorial Hospital from 1940 to 1957, 8 instances of bone metastasis were found. Two additional patients were originally treated elsewhere and were seen for metastatic disease only. The age range was from twenty-eight to sixty-eight years. No correlation with the tumor stage was noted. The interval between treatment of the primary cervical cancer and the onset of bone pain was as brief as two months and as long as fourteen years. The most common sites of involvement were the vertebrae and pelvis. Ribs, scapula, and skull were also involved. The lesions were lytic in 8 patients and mixed lytic and blastic in 2 patients. There appear to be three groups into which the skeletal lesions fall: direct extension, lymph node involvement, and hematogenous metastases. In direct extension, the initial changes in pelvic bones are dissolution of the cortex along the sacrosclerotic notch or loss of the ileopsopectineal line. In lymph node metastases, the earliest vertebral changes are a loss of

body substance. Advanced lesions show extensive destruction of adjacent bones, joints, and intervertebral spaces, associated with a large soft tissue mass due to aggressive local invasion and spread. Hematogenous metastases are indistinguishable from those of other neoplasms.

Radionecrosis of bone was seen in 7 patients following irradiation for carcinoma of the cervix. The interval from therapy to onset of radionecrosis was one year and three months to five years. The average case was seen at four years \pm six months. The most frequent complication was femoral neck fracture. All of the cases with fracture of the femoral neck had been treated through lateral fields. Two of the 3 cases of severe pubic bone fracture and iliac crest breaks were in patients treated through oblique fields. The estimated dose ranged from 7,000 to 12,000 rads. Radionecrosis of the pelvis is readily distinguishable from metastatic involvement because of the absence of osteolysis and cortical destruction coupled with a predictable pattern of bone sclerosis and fracture in femora, pubis, and ilia depending on portal arrangement.—*A. W. Sommer, M.D.*

RADIOISOTOPES

ROSENBERG, I. N., and CHALFEN, M. H. Effect of thyrotropin upon release of iodide from human and rat thyroid. *J. Clin. Endocrinol. & Metabol.*, 1961, 21, 554–568. (From: The Research Laboratories of the Fifth and Sixth [Boston University] Medical Services, Boston City Hospital and the Department of Medicine, Boston University School of Medicine, Boston, Mass.)

The effects of thyrotropin (TSH) administration in man and rats were studied with regards to (a) the urinary excretion of radioiodine after glandular iodine stores had been labeled by I^{131} , and (b) the concentration of radioiodide within the thyroid under varying experimental conditions. There were 14 patients of which 10 were euthyroid, 2 were thyrotoxic, and 2 were myxedematous.

The injection of TSH led to a prompt increase in urinary I^{131} in both man and the normal rat. The administration of TSH to perchlorated treated euthyroid or hyperthyroid human subjects, who had been given I^{131} several days earlier, showed a 2 to 6 fold increase in urinary excretion of I^{131} . The results were similar after therapy with propylthiouracil had been started. This was due in part to a further inhibition of glandular re-utilization of labeled iodide arising from peripheral degradation of thyroid hormone. The perchlorate alone caused an increase in urinary I^{131} , but it was less than that with TSH. The urinary I^{131} in both pre-TSH and post-TSH periods behaved like iodide and was almost completely removed from acidified urine in an anion exchange

resin. No change occurred in urinary I^{131} after injection of TSH in the 2 myxedematous cases.

The administration of TSH to patients pre-treated with methimazole (tapazole) alone usually failed to produce a striking early change in glandular radioactivity as measured by external counting techniques.

A small quantity of thiocyanate was given to 8 cases together with the initial dose of methimazole in order to decrease, but not eliminate, the thyroid-plasma iodide- I^{131} gradient. A transient decrease in glandular radioactivity was observed after the injection of TSH in 5 of the cases. The methimazole prevents organic binding and the thiocyanate impairs the iodide trapping. Studies on the rats produced approximately the same results as in humans. Injection of TSH produced a decrease in activity of I^{131} in the rat thyroid when the organic binding of I^{131} was blocked by propylthiouracil and the thyroidal iodine stores were unlabeled. The percentage of iodide- I^{131} in glands, in which the organic iodine stores had been labeled and in which the organic binding was not blocked, increased after TSH was injected.

The above tests give support to the hypothesis that the administration of TSH produces an increase in the intrathyroidal concentration of iodide derived from deiodination reactions and that the iodide produced may be released from the gland.—C. W. Cooley, M.D.

FRETHEM, ALLEN A., ALBERT, A., and KEATING, F. RAYMOND, JR. Iodine metabolism in surviving thyroid slices from patients with exophthalmic goiter. *J. Clin. Endocrinol. & Metabol.*, 1961, 21, 849-855. (From: Sections of Medicine and Physiology, Mayo Clinic and Mayo Foundation, Rochester, Minn.)

Iodine metabolism in surviving thyroid tissue slices from 18 patients with exophthalmic goiter and 4 euthyroid cases was studied by means of a modified gravity flow incubation technique using Krebs-Henseleit bicarbonate incubating medium containing 4 μ C of I^{131} per 100 ml. The radioactivity was measured by a scintillation counter connected to a multiscaler. Organically bound I^{131} in the tissue slices was determined by precipitation with trichloroacetic acid. The patients were prepared with Lugol's solution prior to operation.

Iodine metabolism in hyperplastic thyroid tissue differed from that of normal thyroid tissue in that: (a) the pattern of I^{131} uptake in hyperplastic tissue was curvilinear with respect to time, whereas that of normal tissue was rectilinear; (b) the rate of I^{131} uptake was greater in hyperplastic tissue than in normal tissue; and (c) the mean proportion of I^{131} iodine bound to protein in hyperplastic tissue was approximately one-half that in normal tissue.

Methimazole (tapazole) blocked protein binding in both normal and hyperplastic thyroid tissue. Thiocyanate discharged most of the accumulated I^{131} in

both normal and hyperplastic tissue. Inorganic iodides inhibited both I^{131} trapping and protein binding in certain concentrations in hyperplastic tissue. Organic iodide compounds, such as thyroxine, triiodothyronine, diiodotyrosine, and thyroglobulin depressed the I^{131} uptake in normal tissue.—C. W. Cooley, M.D.

McKENZIE, J. M. Studies on the thyroid activator of hyperthyroidism. *J. Clin. Endocrinol. & Metabol.*, 1961, 21, 635-647. (From: McGill University Clinic, Royal Victoria Hospital, Montreal, Canada.)

Excessive secretion of thyrotropin has long been suggested as the cause of hyperthyroidism, but assay results have been conflicting. Within the past few years there has been evidence by bioassay that there may be another substance, which unlike thyrotropin, stimulates the thyroid.

The author has sought this "thyroid activator" in 101 patients. It was found in 8 of 9 persons with exophthalmos and hyperthyroidism; in 19 of 25 persons without exophthalmos but with hyperthyroidism; in 19 of 23 persons with hyperthyroidism in the past but with persisting exophthalmos; in 11 (79 per cent) of 14 persons with the exophthalmos typical of Graves' disease, but with no evident abnormality of thyroid function; and in 1 of 25 persons with no history of exophthalmos or hyperthyroidism.

Extraction of the thyroid activator from serum was done by means of ultrafiltration and starch-block electrophoresis.

The results make it tempting for the author to give pathogenetic significance to the substance (thyroid activator) in the hyperthyroid-exophthalmic complex known as Graves' disease. It seems reasonable that such thyroid activation occurs in the thyroid as a result of the factor in the blood. In order to assign an exophthalmic producing role to the substance, coincident assays for both thyroid activator and exophthalmic producing substance are felt to be necessary to resolve this possibility.

It should be noted that the activator has been found in normals and the author wonders whether such a fact signifies a potential for the onset of Graves' disease.

The author admits that none of the instances of differences between thyroid activator and thyrotropin conclusively proves that the substances are entirely different. The activator may differ only in the manner that it is bound to the plasma proteins. If it is a separate entity, where is its site of origin? Apparently thus far there have been no instances of it being assayed from the pituitary in those with hyperthyroidism (or Graves' disease).—W. K. Littman, M.D.

BUCHANAN, W. WATSON, KOUTRAS, D. A., ALEXANDER, W. D., CROOKS, M., RICHMOND, M. H., MacDONALD, E. M., and

WAYNE, E. J. Iodine metabolism in Hashimoto's thyroiditis. *J. Clin. Endocrinol. & Metabol.*, 1961, 21, 806-816. (From: University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow W1, Scotland.)

Iodine metabolism was studied in 40 patients with untreated Hashimoto's thyroiditis. A combination of isotopic and chemical techniques was used. Some of the tests and the results were: (1) Thyroidal I^{131} uptakes and thyroidal clearance rates were usually within the normal range. High values were found frequently in the 14-hour uptake study which exceeded the 48-hour uptakes in 15 of the 40 cases. This is consistent with a short biologic half-life of I^{131} in Hashimoto's thyroiditis; (2) plasma inorganic iodine levels were within a normal range as were the absolute iodine uptakes; (3) plasma PBI I^{131} levels were above the upper limits of normal and in 11 patients were in the thyrotoxic range; (4) the plasma PBI levels were in the hypothyroid or low normal range; (5) the intrathyroidal exchangeable iodine values were usually abnormally low; (6) the renal clearance of iodide was usually within the normal range; (7) the thyrotropin or TSH test showed a slight increase in I^{131} uptake in 3 of 10 cases. There was a rise of PBI I^{131} after TSH administration. The rise was lower than in normal subjects; (8) the thyroxine suppression tests were normal; and (9) potassium perchlorate discharge tests yielded positive results in 12 of 27 patients.

The results of standard I^{131} tests vary markedly in Hashimoto's thyroiditis. However, a combination of a high plasma PBI I^{131} level, with either a normal thyroidal I^{131} uptake or a low blood plasma PBI level, is of diagnostic value. The potassium perchlorate discharge test is of diagnostic value when it is positive. A low PBI level in a clinically euthyroid patient indicates an early degree of hypothyroidism.

The above tests indicate that the thyroid gland is able to trap a normal quantity of iodine but is unable to utilize it to form thyroid hormone.

The abnormal results often obtained in the standard I^{131} tests in Hashimoto's thyroiditis can be explained by taking into consideration the entire iodine metabolism.—C. W. Cooley, M.D.

LEBOEUF, GILLES, BONGIOVANNI, ALFRED M., STEIKER, DANIEL D., and EBERLEIN, WALTER R. Immunologic and thyroid function studies in euthyroid children with goiter. *J. Pediat.*, Apr., 1961, 58, 477-481. (From: The Children's Hospital of Philadelphia, Department of Pediatrics, School of Medicine, University of Pennsylvania, Philadelphia, Pa.)

Between January, 1955, and January, 1960, 41 clinically euthyroid children were referred to the Endocrine Clinic of the Children's Hospital of Phila-

delphia because of a goiter. These children were studied both with the standard tests of thyroid function and with recently devised immunologic techniques to detect the presence in the serum of antibodies which react with human thyroid extracts. In some, the serum was also studied for abnormal protein patterns, and in a few patients an open biopsy of the thyroid was performed. The results of these studies suggest that, in that locality, goiters in euthyroid children are most commonly associated with an autoimmune process directed against the thyroid gland.

Protein bound iodine (PBI) and serum butanol-extractable iodine (BEI) studies were made. I^{131} uptakes were measured with a scintillation counter twenty-four hours after the administration of 1 to 7 mc of the isotope. In some patients the uptake study was repeated after the intramuscular injection of 2.5 units of thyrotropin (TSH) every twelve hours for a total of 4 doses. The uptake could not be correlated with the PBI or BEI in many instances. Initially, serum thyroid-agglutinating antibodies were assayed by this method and, subsequently, Witebsky's method was employed.

The most striking and consistent abnormal laboratory finding in this group of 31 children with goiters was the presence of antibodies to human thyroid extracts in the serum of all but 4 patients. While antibodies can be detected in the serum of patients with many different types of thyroid disease, high titers are found almost exclusively in patients with thyrotoxicosis, spontaneous myxedema, and lymphocytic thyroiditis. Since 87 per cent of the children with unexplained goiters in this series had antibodies in their serum and were clinically euthyroid, it might seem reasonable to assume that most of them had thyroiditis. The goiter in each patient gradually regressed in response to treatment with desiccated thyroid, lending further support to this diagnosis.

Unfortunately, none of the available tests is specific for thyroiditis, the diagnosis of which can only be made histologically. The detection of thyroid antibodies in the serum of most of these children with unexplained goiters can, therefore, be taken as proof only of the presence of an autoimmune process involving the thyroid gland, not of thyroiditis.

If the results of the very small number of biopsies performed in this series can be considered representative of what would have been found in the others, it seems justified to conclude that in that locality most, but not all, euthyroid children with a goiter had a form of chronic thyroiditis.—Paul L. Webster, M.D.

BONNET, JOHN D., HIGHTOWER, NICHOLAS C., JR., PETRANY, ZOLTAN, and SOMMER, ARNO W. A simple direct method for determining radioactivity in feces. *Am. J. Digest. Dis.*, 1961, 6, 520-525. (Address: J. D. Bonnet, Scott & White Clinic, Temple, Tex.)

Standard procedures for quantitative analysis of stool specimens, either chemical or radioactive, require weighing, dilution and homogenization of feces, in addition to analysis in duplicate or triplicate. In this report, the authors describe the application of the method originally described by Owen which determines radioactivity in feces by a rapid simple direct approach.

Clinically, sodium radioiodide, radioiodinated triolein, radioiodinated oleic acid, radiochromium and radioiron have been used.

Homogeneity of the stool specimen is obtained by collecting each stool specimen individually without pooling.

The principle employed in the method is that the number of counts from any amount of radioisotope collected and packed in a standard carton will vary only with the height of the specimen. After measuring the activity of the specimen, correction tables are employed to give a corrected net count at zero volume. A pilot, prepared from a portion of the dose of radioisotope administered to the patient, is counted when the radioactivity of the stool specimen is determined and corrected to zero volume. Final calculation is by the following formula:

$$\begin{aligned} \% \text{ dose in feces} &= \frac{\text{corrected net cps for specimen} \times 100}{\text{corrected net cps pilot} \times \text{dose factor}} \end{aligned}$$

Variation of determinations from the dose administered was no greater than 1 per cent as compared to standard sample-size methods.—George A. Miller, M.D.

BARLOW, C. F., DOMEK, N. S., GOLDBERG, M. A., and ROTH, L. J. Extracellular brain space measured by S^{35} sulfate. *A.M.A. Arch. Neurol.*, 1961, 5, 102-110. (From: Department of Medicine (Neurology) and Department of Pharmacology, The University of Chicago, Chicago, Ill.)

Electron microscopic studies of the central nervous system have illustrated the virtual absence of detectable extracellular spaces. Such a fact makes disputable the existence of the chloride ion as an indicator of the extracellular space of brain as this would presume a compartment of approximately 30 per cent of brain weight.

The present study is an attempt to measure the extracellular space, if one exists. S^{35} was used in studying ureter-ligated adult and immature cats by gross autoradiography and radioassay methods. Correction for metabolic incorporation was made.

All anatomic structures studied in the brain of the adult cat were found to have a sulfate space of approximately 2 to 4 per cent. Metabolic incorporation

calculations did not alter the values. By contrast the kittens prior to the age of three months showed as high a sulfate space as 33.5 per cent in white matter and 16.8 per cent in cerebral cortex.

The question is posed as to whether the sulfate space actually represents the extracellular space of the brain. Previous experiments seem to lend support to the fact that sulfate is primarily an extracellular ion in the body in general. There is no absolute proof.

The conclusion is that the findings are in more general agreement with the electron microscopic findings. The authors do not agree that the extracellular space does not exist, but believe that it is approximately 4 per cent of the wet weight of the brain. Previous chloride space studies indicate that a portion of brain chloride is probably intracellular and that their studies are more likely to reflect a true expression of the extracellular spaces than previous chloride space studies which were done *in vitro* on excised tissues.

Microscopic studies do show the existence of an extracellular space in immature animals, which agrees with the present study. This may help explain why in the immature animal there is easier access to the brain of many blood borne substances at that age.—W. K. Littman, M.D.

FREY, ENRICO, MATTER, HANS, and PESTALOZZI, DAVID. Transnasale Spickung eines vorwiegend suprasellären Hypophysentumors mit Yttrium-90-rods. (Transnasal implantation of yttrium 90 rods in a largely suprasellar, hypophyseal tumor.) *Strahlentherapie*, Feb., 1961, 114, 239-247. (From: Radiotherapeutische Klinik und Poliklinik und Augenklinik der Universität, Zürich, Switzerland.)

A large, mainly suprasellar, hypophyseal tumor produced progressively more optic chiasmal symptoms in a sixty-seven year old man in spite of a tumor dose of 6,000 r from a cobalt teletherapy unit. The patient refused surgical treatment. Six yttrium 90 rods (2.5 mc each) were introduced transnasally and transsphenoidally, three into each side of the sellar-suprasellar region on May 6, 1960. This yielded approximately 20,000 rads at the center of the treated volume and 3,000-5,000 rads at the periphery of the tumor as demonstrated on a pre-operative air encephalogram. The patient gradually improved; in two months his visual fields were enlarging. Re-examination on September 26, 1960 showed that his visual fields had become considerably larger, enough so that he could again be gainfully employed without hazard, and skull roentgenograms showed that the yttrium 90 rods had shifted with shrinking of the tumor, to lie almost entirely within the sella.—Henry G. Moehring, M.D.



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Atomic Energy of Canada Ltd.	xxxv
Baird-Atomic, Inc.	xx
Barnes-Hind Barium Products, Inc.	xlili
Bell-Craig, Inc.	xxvii
British Institute of Radiology	lii
Campbell X-Ray Corporation	xl
Continental X-Ray Corporation	xxii
Cee Bee Services	xxxv
Dunlee Corporation	xlii
Eastman Kodak Company	xlvi, xlv
Fisher Scientific Company	xiv
Fougera, E. & Company, Inc.	xiv, xv
General Electric Company	xxviii, xxix, xxx, xxxi, xxxvi, xxxvii
Hanley Medical Equipment Company	li
High Voltage Engineering Corp.	Third cover
Philip A. Hunt Company	xxxiv
Ilford, Inc.	viii
Karger, S.	xlvi, xlviii, xlix
Liberty Protective Leathers, Inc.	xl
Low X-Ray Corporation	xli
Machlett Laboratories	xxlii
McElroy, Donald, Inc.	xl
Mullard Equipment Limited	xxvi
Nuclear-Chicago Corporation	ix, x, xi, xii
Pako Corporation	xxxviii
Pickier X-Ray Corporation	vii, xxxiii, Fourth cover
Profexray, Inc.	i
Schick X-Ray Company	Second cover
Siemens-New York, Inc.	xxxix
Squibb, E. R. & Sons	v
Standard X-Ray Company	vi
Thomas, Charles C, Publisher	xlii, li
Victoreen Instrument Company, The	xxxii
Westinghouse Electric Company	xliv
Winthrop Laboratories	xviii, xix
Wolf X-Ray Products, Inc.	xxi



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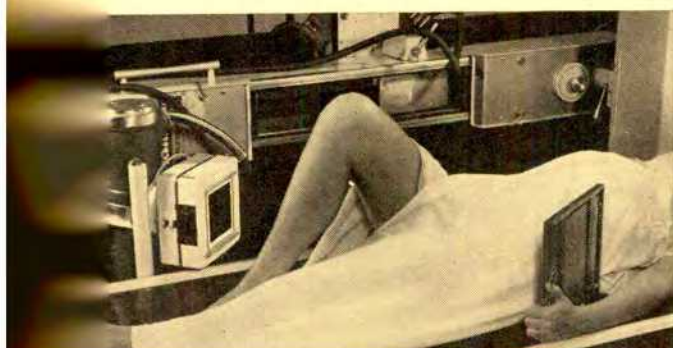
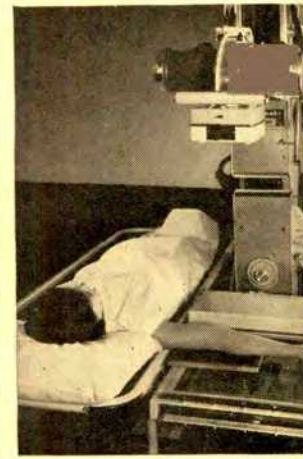
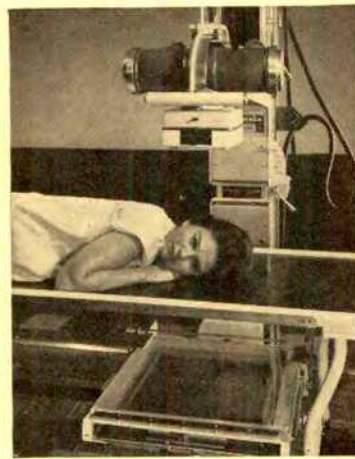
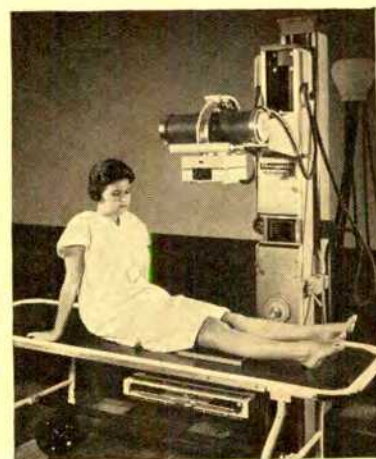
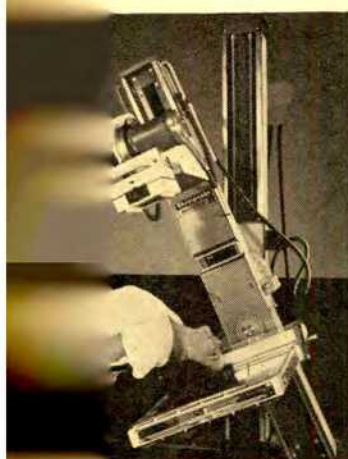
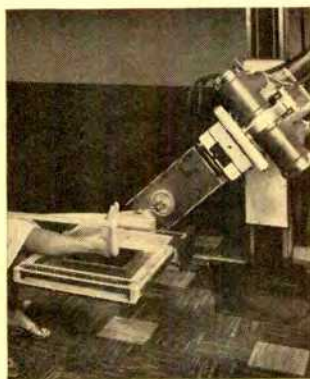
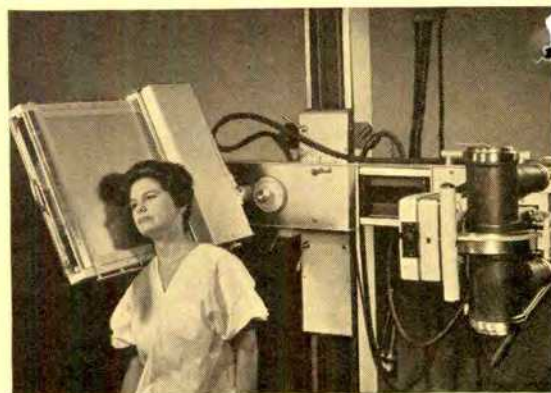
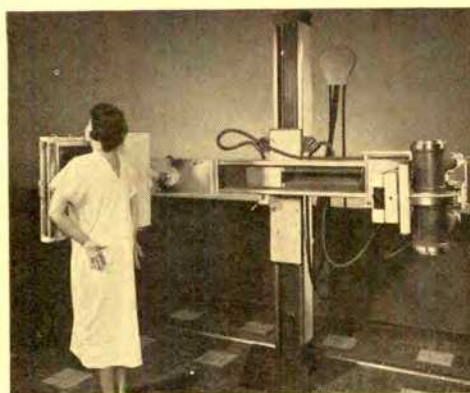
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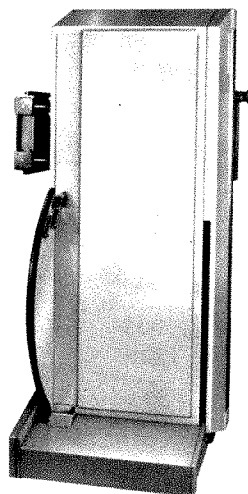
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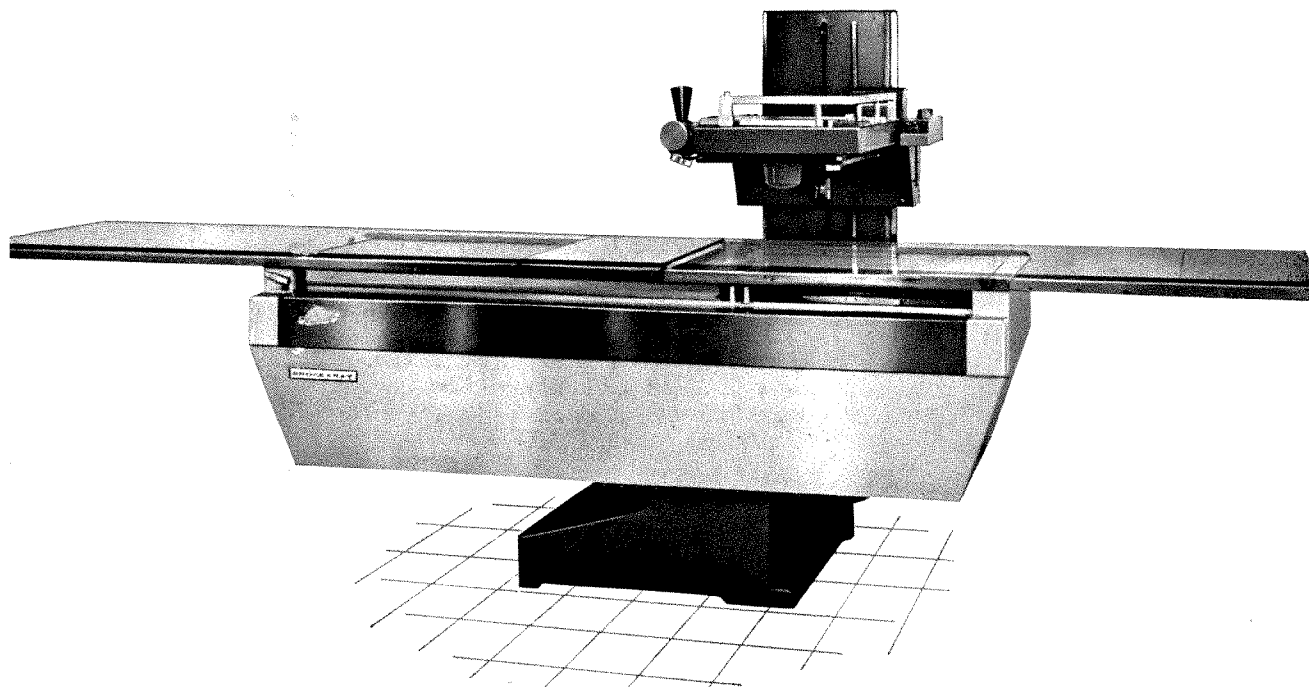
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Vol. 87

MARCH, 1962

No. 3

CONTENTS

<i>Oral Cancer: A Twenty-Five Year Study. Janeway Lecture, 1961.</i> CLIFFORD L. ASH, M.D.	417
<i>Necrosis in Treatment of Intraoral Cancer by Radiation Therapy.</i> WILLIAM S. MACCOMB, M.D.	431
<i>Distant Metastases from Head and Neck Cancer.</i> SIDNEY RUBENFELD, M.D., GUSTAVE KAPLAN, M.D., AND ADRIAN A. HOLDER, M.D.	441
<i>Localization of Brain Tumors Using Radioiodinated Human Serum Albumin.</i> EDWARD B. SCHLESINGER, M.D., SHEILA DEBOVES, B.A., AND JUAN TAVERAS, M.D.	449
<i>Radiation Therapy in the Treatment of Intracranial Tumors.</i> ROBERT J. BLOOR, M.D., ARCH W. TEMPLETON, M.D., AND RAYMOND S. QUICK, B.Sc.	463
<i>Should We Treat Glioblastoma Multiforme? A Study of Survival in 425 Cases.</i> JUAN M. TAVERAS, M.D., HARTWELL G. THOMPSON, JR., M.D., AND J. LAWRENCE POOL, M.D.	473
<i>The Radium Treatment of Recurrent Cancer of the Uterine Cervix.</i> J. ERNEST BREED, B.S., M.D.	480
<i>Comparative Study of Supervoltage Radiotherapy Techniques in Some Pelvic Malignancies.</i> JOSÉ NORIEGA L., M.D., D.M.R. (London), AND ARMANDO LÓPEZ, M.D.	488
<i>Isodose Curves and Radiation Distribution about Patients with Intracavitary Radium Sources.</i> HANS-GUENTER WANDEL, M.D.	500
<i>Radiotherapy of Ewing's Sarcoma.</i> PAUL W. SCANLON, M.D.	504
<i>Clinical Use of Short Source-Skin Distance Cesium 137 Teletherapy Unit.</i> GILBERT H. FLETCHER, M.D., GORDON C. JOHNSON, M.D., WARREN K. SINCLAIR, PH.D., AND ARTHUR COLE, PH.D.	511
<i>A Cesium Head and Neck Unit.</i> M. LEDERMAN, M.B., D.M.R.E., F.F.R.	521
<i>Common Medical Problems in Radiotherapy Patients.</i> ARVIN S. GLICKSMAN, M.D.	525

(Continued on p. iv)

<i>Hemipelvectomy in the Treatment of Advanced Cancer.</i>	
THEODORE R. MILLER, M.D.	531
<i>Effects of the Combined Action of Roentgen Rays and a Chemical Carcinogen (DAB) on the Rat's Liver.</i> ANTOINE LACASSAGNE, AND	
LUCIENNE HURST	536
<i>The Systemic Effects of Localized Radiation on Serum Proteins in Humans; A Preliminary Report.</i> JOSEPH L. ACKERMAN, M.D.,	
JOSEPH A. LINSK, M.D., AND BERNARD J. SHUMAN, M.D.	543
<i>Postirradiation Treatment of Lethal Total Body Irradiation by Cell-Free Spleen Extracts.</i> FRIEDRICH ELLINGER, M.D.	547
<i>Preliminary Reports of Chromosome Studies during Radiation Therapy.</i>	
ROBERT C. GOODLIN, M.D.	555
<i>Low Levels of X-Irradiation and the Early Mammalian Embryo.</i>	
ROBERTS RUGH	559
<i>The Influence of the Time Factor on the Dose-Response Curve.</i>	
LUCILLE A. DU SAULT	567
<i>The Second Half-Value Layer and the Homogeneity Coefficient.</i> E. DALE	
TROUT, B.S., D.Sc., JOHN P. KELLEY, B.S., AND ARTHUR C. LUCAS, B.S.	574
<i>Dosimetry by Tomography in Interstitial Curitherapy: Point Technique.</i>	
B. PIERQUIN, M.D., AND J. V. FAYOS, M.D.	585
<i>World Survey of Radioisotope Teletherapy Units.</i> K. C. TSIEN	593
<i>Officers</i>	600
<i>Editorials</i>	
<i>A Concept of Radiosensitivity.</i> J. ROBERT ANDREWS	601
<i>The Undergraduate Teaching of Radiation Therapy.</i>	
PHILIP RUBIN, M.D.	606
<i>Gioacchino Failla, 1891-1961.</i> HARALD H. ROSSI, Ph.D.	608
<i>News Items</i>	611
<i>National Bureau of Standards; Scattering from a Cobalt 60 Calibrating Source</i>	612
<i>Book Reviews</i>	614
<i>Books Received</i>	616
<i>Society Proceedings</i>	617
<i>Abstracts of Radiological Literature</i>	622

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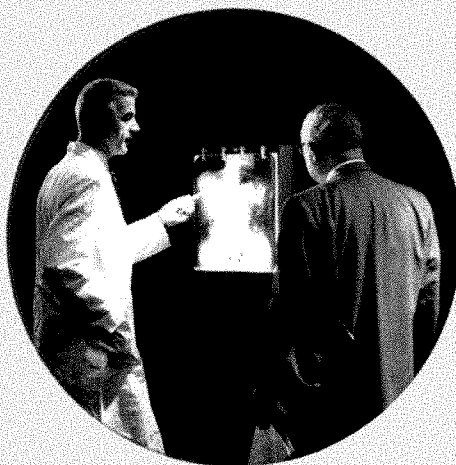
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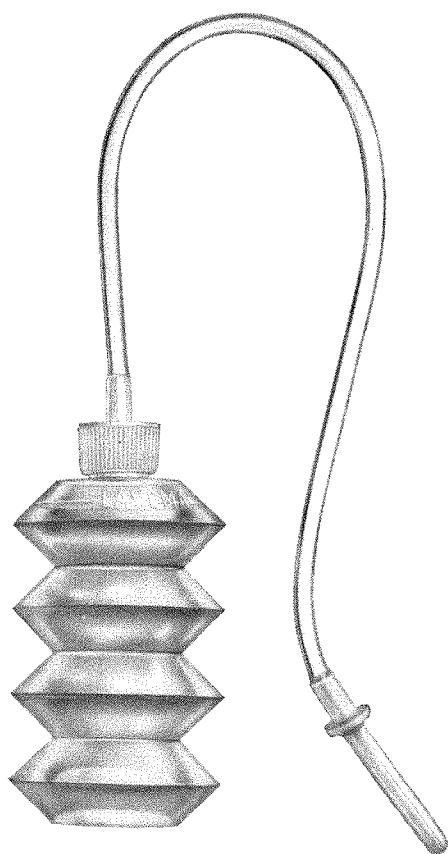
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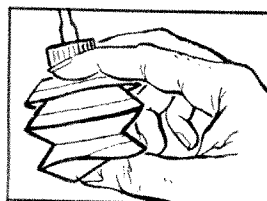


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ORAL CANCER: A TWENTY-FIVE YEAR STUDY*

JANEWAY LECTURE, 1961

By CLIFFORD L. ASH, M.D.
TORONTO, ONTARIO, CANADA

To have been chosen Janeway Lecturer for 1961 is indeed a great honor, particularly so as I believe that I am the first Canadian and the second person outside the United States to whom this privilege has been extended. Dr. Henry Harrington Janeway (1873-1921) epitomizes the type of early worker in radiation therapy to whom we, the present generation, owe so much. In the first Janeway Lecture delivered before this Society in 1933 Dr. James Ewing described Dr. Janeway's success as being due to his scientific imagination, indomitable will, untiring industry, excellent surgical training, and a strong confidence in the ultimate capacity of radiation to control cancer.

Dr. Janeway, I feel, would be pleased to be with us today because the subject that I have chosen is a splendid example of the application of his own particular interest and belief; namely, the coordinated efforts of surgery and radiation therapy in the treatment of malignant disease. For my own part I wish to express my indebtedness to my teacher, the late Dr. Gordon E. Richards, to his and my surgical colleagues, so well represented by Dr. Harold Wookey, whose combined efforts in

the management of oral carcinoma form the basis of much of the material that I wish to present today. In choosing the subject of oral cancer it was realized that this had been covered in the Janeway Lecture of last year under the broader title of "Head and Neck Cancer": in no sense do I intend to compete with, but rather hope to complement, what Dr. MacComb had to say to you at that time.

THE era following the death of Dr. Janeway was marked by such a rapid increase in medical knowledge and complexities of practice in the fields of medicine, surgery, obstetrics and gynecology, and radiation therapy as related to the management of malignant disease that it became obvious that, unless there was close cooperation between these various specialty groups, there would be a very real danger of development of opposing schools of thought. As an alternative, it was believed that by a combination of effort the true role of each form of treatment in the management of malignant disease would be determined and in this manner the best interests of the patient would be served. Ac-

* Presented at the Forty-third Annual Meeting of the American Radium Society, Colorado Springs, Colorado, May 11-13, 1961.

cordingly, combined clinics were established in the Department of Radiotherapy at the Toronto General Hospital at which representatives from the interested specialties were in attendance, not only for the purpose of seeing new patients, but to take part in the follow-up of old patients as well. The oral clinic for example, had in attendance not only a radiotherapist, but also a surgeon interested in "head and neck" problems and a dental surgeon. In this manner treatment policies were evolved.

With the rapid development of radiotherapeutic methods and equipment following the last war, and particularly with the availability of supervoltage equipment such as cobalt 60 units for therapy, a decision had to be reached as to whether or not individual hospitals could justifiably maintain fully equipped radiotherapeutic departments from an economic point of view, based on the case load. In 1949, at the request of the Provincial Government, the President of the University of Toronto set up a committee to study this problem in relation to the teaching hospitals in Toronto. From this group a recommendation was made that a centralized Institute of Radiotherapy should be established, which would be common to the teaching hospitals. This recommendation was implemented and has now materialized in the form of The Ontario Cancer Institute, which incorporates under the same roof not only The Princess Margaret Hospital, but also Divisions of Biological and Physics Research. It is indeed an experiment in cooperation. Under the aegis of the University five teaching hospitals, in addition to our own, are pooling their resources in an effort to give patients the best treatment possible. An added impetus to our work is the stimulation afforded by the research divisions, which together form the nucleus for the Department of Biophysics of the University of Toronto.

Although radiotherapy is the main form of treatment in this institution, other forms of therapy, *excluding* major surgery, are

also used. Surgical treatment, in our opinion, is better carried out at the associated general hospitals from which the patients have been referred. Our oral clinic, as presently constituted, is attended by staff radiotherapists, "head and neck" surgeons from each of the three major teaching hospitals, and dental consultants from the School of Dentistry of the University.

To place the problem in perspective, it is of interest to note that in Canada the incidence of intra-oral cancer is approximately 4.0 for males and 1.2 for females per 100,000 population. The incidence in males is somewhat lower than that reported by Dorn (7.0) for the white population of the United States. The incidence in females reported by Dorn (2.0) is comparable to our experience in Canada. In one province of Canada, in which cancer is a registrable disease, intra-oral cancer constituted approximately 2.5 per cent of the total of 18,138 cases. Of all cancer deaths in Canada intra-oral cancer accounts for 3 per cent in males and 1.1 per cent in females. These figures, however, include cases of cancer of the lip, which would make them slightly higher than they probably are.

The present study is based on all cases registered, whether treated or not, of squamous cell carcinoma, or its variants, which have not received previous treatment and which were judged to have originated in the tongue, buccal mucosa, gingiva, floor of mouth, and palate; but does not include carcinomas of the lip, tonsil, or oropharynx. Between the years 1929 and 1958, 1,944 cases in this category were registered. The distribution of these by site is shown in Table I.

The average age and sex distribution are indicated in Table II. Although oral carcinoma continues to occur predominantly in males, there has been a definite change in the sex distribution for most sites analyzed by decade. Figure 1 shows the percentage distribution for male and female. It is to be noted that in carcinoma of the tongue, the male-female ratio dropped from 4:1 for the

TABLE I
DISTRIBUTION BY SITE, 1929-1958

Site	No. of Cases
Tongue	763
Buccal mucosa	406
Gingiva	423
Floor of mouth	219
Palate	133
All cases	1,944

early years to 2:1 for the last decade of the study. A similar change is noted for gingival and floor of the mouth lesions.

Possible predisposing or etiological factors (Table III) were recorded in 68 per cent of the cases, and no statement was made as to their presence or not in another 19 per cent. It is interesting to note that syphilitic infection was present in but 4.6 per cent of cases, and most of these occurred in the earlier years of the study. However, this infection should continue to be borne in mind when assessing oral lesions. Within the past six months the case shown in Figure 2 was seen in our clinic and the presence of syphilitic infection was not suspected by the more junior members of the staff, although to those of us who had seen such lesions when syphilis was relatively more common, it would have been immediately thought of. In 43 cases of carcinoma of the tongue that subsequently developed multiple intra-oral primary le-

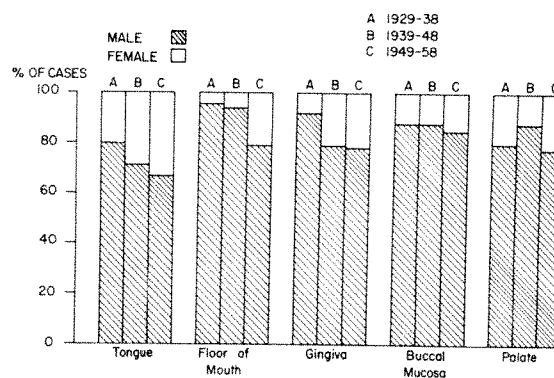


FIG. 1. Percentage distribution by sex and decade. Intra-oral cancer, 1929-1958.

sions, one or other of the above factors were recorded in all but 14 cases.

STAGING

The staging used in the tables here included represents the stage of the primary lesion when first seen according to the Richards classification. This classification has been employed in our entire series and was first presented at the Forty-first Annual Meeting of the American Roentgen Ray Society in 1940. It is essentially the same system as now proposed by the International Union Against Cancer, using a TNM nomenclature in which the primary and secondary lesions are staged sepa-

TABLE III
ORAL CARCINOMA, 1929-1958
RECORDED ETIOLOGICAL FACTORS

TABLE II
AVERAGE AGE AND SEX DISTRIBUTION, 1929-1958

Site	No. of Cases	Per Cent		Average Age	
		Male	Female	Male	Female
Tongue	763	71.3	28.7	64.5	65.0
Buccal mucosa	406	87.2	12.8	67.7	64.1
Gingiva	423	82.0	18.0	67.8	67.2
Floor of mouth	219	86.8	13.2	65.2	60.9
Palate	133	82.0	18.0	65.2	61.0
Total	1,944	79.4	20.6	66.1	64.8

Etiology	Per Cent
Trauma (dental, mechanical)	13.8
Tobacco	13.7
Leukoplakia	8.7
Syphilis alone	2.5
Syphilis with other factor	2.1
Alcohol	1.8
Anemia	0.8
Chronic inflammation	1.0
Other, or combination	23.8
Not stated	19.1
None	12.7

—68.2

31.8

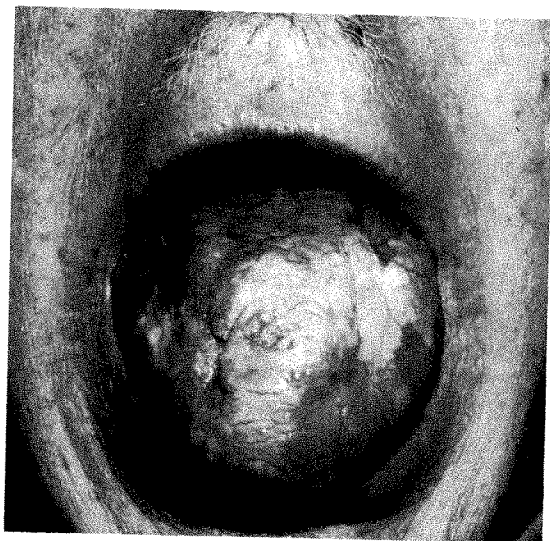


FIG. 2. Syphilitic tongue with squamous cell carcinoma change on right side.

rately. Tables IV and V give the details of the two classifications.

To determine the effect that the proposed international staging would have on our material, the cases were re-staged according to this method. A comparison of the two systems is shown in Tables VI and

TABLE IV

THE RICHARDS CLASSIFICATION

1. *Primary Lesion*

- Stage I—A unilateral or single lesion measuring not more than 1.5 cm. in diameter
 Stage II—A lesion not larger than 3 cm. in diameter with a corresponding degree of ulceration or infiltration
 Stage III—A lesion greater than 3 cm. and/or invading adjacent structures
 Stage IV—A lesion characterized by massive involvement of the region and gross extension to adjacent structures or bone

2. *Secondary Involvement*

- Stage I—Small, discrete, movable, unilateral, operable
 Stage II—Larger, up to the size of olives, still discrete, unilateral *or* lymph nodes as described in (1) but which are bilateral, operable
 Stage III—Massive metastatic carcinoma in lymph nodes, matted and immovable, may be unilateral or bilateral, inoperable

TABLE V

U.I.C.C. PROPOSAL FOR TNM CATEGORIES, ORAL CAVITY

T—*Primary Tumor*

- T₁—Tumor of 1 cm. or less in its greatest dimension
 —Limited to one region—Mobility not affected
 T₂—Tumor more than 1 cm. but not more than 2 cm. in its greatest dimension
 —Limited to one region—Mobility not affected
 T₃—Tumor more than 2 cm. but not more than 5 cm. in its greatest dimension
or Tumor invading more than one region
or Tumor invading muscle with limitation of mobility
 T₄—Tumor of more than 5 cm. in its greatest dimension
or Tumor invading neighboring organs or bone

N—*Regional Lymph Nodes*

- N₀—No regional lymph nodes palpable
 N₁—Homolateral lymph nodes palpable but movable
 N₂—Contralateral or bilateral lymph nodes palpable but movable
 N₃—Fixed lymph nodes

M—*Distant Metastasis*

- M₀—No evidence of metastasis
 M—Distant metastasis present

VII. It is to be noted that the limitation of 1 cm. as the upper limit of Stage I lesions and 2 cm. as that for Stage II tends to place the bulk of the material to be classified in Stages III and IV. As a result, division of the cases into early lesions, comprising Stages I and II, and late lesions, comprising Stages III and IV, places a large proportion of the cases in these latter stages, whereas in the system currently in use the division between early and late stages was more nearly equal and, for purposes of comparison with surgical results would, in the author's opinion, seem to lend itself better to the division between operable and inoperable cases.

FIVE YEAR SURVIVAL RATES

Of the 1,944 cases only 1,729 are available for estimate of five year survival. Survival rates are usually computed as either crude or adjusted. Crude survival rate (CSR) is the percentage of patients

TABLE VI
ORAL CARCINOMA, 1929-1958
COMPARISON OF STAGING METHODS

Site	Primary Lesion									
	R _I	T _I	R _{II}	T ₂	R _{III}	T ₃	R _{IV}	T ₄	R. N.S.	T. N.S.
Tongue	151	80	245	173	224	366	135	137	8	7
Buccal mucosa	82	30	141	59	111	194	64	100	8	23
Gingiva	45	18	119	61	134	203	122	133	3	8
Floor of mouth	34	20	82	46	60	117	37	32	6	4
Palate	19	7	42	18	41	60	29	44	2	4
All sites	331	155	629	357	570	940	387	446	27	46

TABLE VII
ORAL CARCINOMA, 1929-1958
COMPARISON OF STAGING METHODS

Site	Lymph Nodes							
	R _I	N _I	R _{II}	N ₂	R _{III}	N ₃	R. N.S.	T. N.S.
Tongue	115	126	39	29	100	101	2	0
Buccal mucosa	57	58	3	3	40	40	5	4
Gingiva	96	96	7	8	38	37	1	1
Floor of mouth	27	36	17	6	27	34	6	1
Palate	18	17	6	10	6	8	5	0
All sites	313	333	72	56	211	220	19	6

TABLE VIII
CRUDE FIVE YEAR SURVIVAL RATES BY SITE AND STAGE, 1929-1955

Site	No. of Cases	Stage of Primary					All Stages %
		I %	II %	III %	IV %	n. s. %	
Tongue	671	51.9	37.0	21.2	8.1	*	30.0
Buccal mucosa	374	53.8	42.8	29.5	5.3	*	35.3
Gingiva	383	45.0	40.4	24.6	22.7	*	30.5
Floor of mouth	184	59.4	47.0	28.8	20.7	*	40.2
Palate	117	62.5	28.2	18.4	13.6	*	26.5
All cases	1,729	52.8	39.6	24.2	14.0	20.8	32.1

* Rates not calculated for fewer than 10 cases.

TABLE IX
NET FIVE YEAR SURVIVAL RATES BY SITE AND STAGE, 1929-1955

Site	No. of Cases	Stage of Primary					All Stages %
		I %	II %	III %	IV %	n. s. %	
Tongue	671	65.7	45.7	23.2	8.4	*	34.8
Buccal mucosa	374	78.2	62.1	36.9	6.4	*	47.6
Gingiva	383	54.5	50.6	31.0	28.1	*	38.0
Floor of mouth	184	73.1	57.4	31.9	21.4	*	46.5
Palate	117	83.3	35.5	24.1	16.7	*	34.1
All cases	1,729	68.8	50.7	28.5	15.9	27.8	39.3

* Rates not calculated for fewer than 10 cases.

under observation who were alive and traced at the end of N years. The adjusted survival rate (ASR) is the percentage of the expected number of survivors at N years, based on prevailing mortality rates, who were alive at the end of N years. This is usually computed as $CSR \cdot P_0$, where P_0 is the probability of survival for N years calculated from the appropriate life table. Table VIII indicates the crude survival rate for each site. There was a 96 per cent follow up in our material.

Table IX shows the net survival rates which result when the 62 untraced cases and the 254 cases dying of extraneous diseases were excluded. Finally Table X indicates the adjusted survival rates and gives a clearer picture as to what has been accomplished by treatment. It is to be

emphasized that the survivals shown are based on the stage of the primary lesions when first seen and represent the results obtained by the treatment policy which is practiced in our clinic and which has gradually evolved over the past thirty years.

TREATMENT POLICY

In general, the treatment policy has been that the primary intra-oral lesions are managed by radiotherapy, while the metastatic nodes in the neck, wherever possible are dealt with by surgical measures, preferably radical neck dissection. There are, of course, exceptions and occasionally very early primary lesions have been excised as the initial treatment; however, in most cases, surgical treatment of the primary lesion has been employed for residual

TABLE X
ADJUSTED FIVE YEAR SURVIVAL RATES BY SITE AND STAGE, 1929-1955

Site	No. of Cases	Stage of Primary					All Stages %
		I %	II %	III %	IV %	n. s. %	
Tongue	671	68.3	45.7	27.5	10.5	*	38.5
Buccal mucosa	374	68.1	56.3	39.9	7.1	*	47.1
Gingiva	383	62.5	54.6	33.7	29.9	*	41.2
Floor of mouth	184	70.7	61.0	41.1	27.6	*	54.3
Palate	117	75.3	34.8	24.9	18.4	*	34.9
All cases	1,729	68.6	50.8	32.3	18.4	29.7	42.2

* Rates not calculated for fewer than 10 cases.

disease following radiotherapy, or for the complications of it, such as chronic ulcer, or where there is persistent bone involvement, or bone necrosis. On the other hand, radiotherapy has been used in the treatment of neck nodes in patients who are either technically or physically inoperable or, not uncommonly following neck dissection, where it is considered that residual disease might still be present. Even in the more advanced cases of carcinoma of the gingiva with bone involvement, and particularly since the advent of cobalt therapy, irradiation is employed as the initial treatment. In such instances the intent is to limit the disease and is regarded as a preoperative measure to be followed by surgery at a later date when necessary.

METHODS OF TREATMENT

During the period under review, marked changes and improvements have occurred in both the surgical and radiotherapeutic management. The field of surgery has been extended by improved anesthesia, antibiotics and the development of newer techniques. In radiotherapy the major advances have been made in a better appre-

ciation of radiobiological effects and a more detailed knowledge of the natural history and behavior of malignancies generally; finally, the equipment and facilities for the delivery of the radiotherapy have improved markedly. In the earlier part of the period under review, treatment usually took the form of one or other of the then recognized methods of applying radium, as tubes, molds or packs, needles, and radon seeds. In 1934, a 4 gm. Sievert teleradium unit was installed and in 1938, a major change in treatment procedures occurred with the addition of roentgen rays of 400 kv. having a treatment distance of 100 cm. and a half-value layer of 4.5 cm. of copper. At this time, too, an intra-oral cone attachment was installed on a 200 kv. machine. In the period 1938 to 1953, treatment was usually given by a combination of external irradiation at 400 kv., supplemented either by an intra-oral cone, or by a radium needle implant or, very occasionally, by an intra-oral radium mold. With the advent of 400 kv. it was possible to deliver a tumor lethal dose to the area with less risk of tissue and bone necroses (Fig. 3, *A* and *B*; and 4, *A* and *B*). In 1949,

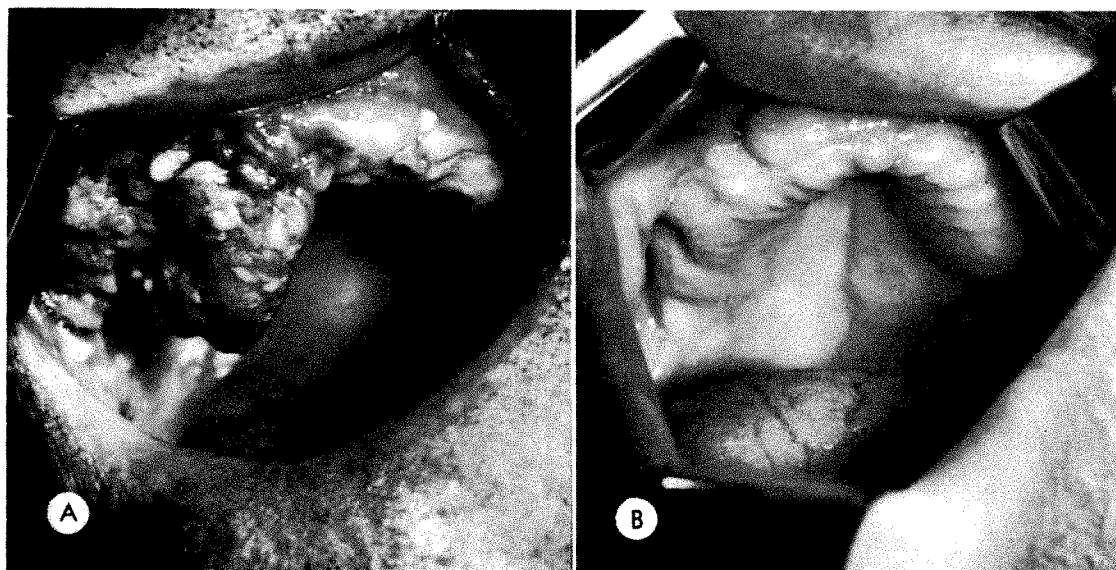


FIG. 3. Extensive carcinoma of the left upper alveolus. Treatment was given in 1941 with 400 kv. roentgen rays plus intra-oral cone. (*A*) Pretreatment. (*B*) Three months post treatment. The lesion remained healed until the patient died in 1948 from another primary carcinoma.

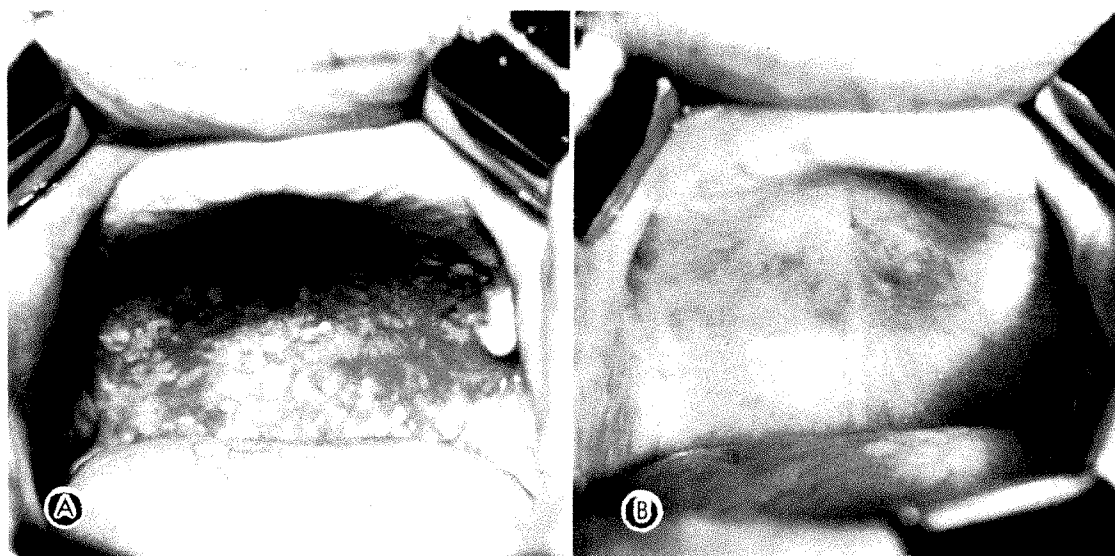


FIG. 4. Carcinoma of the hard palate. Treatment was given in 1941 with 400 kv. roentgen rays plus intra-oral cone. (A) Pretreatment. (B) Four months post treatment. The lesion remained healed until death in 1946.

half-strength radium needles were obtained for use in the central portion of the radium implants and as a result, the incidence of chronic ulcer following such treatment diminished (Fig. 5, *A-C*). In 1953, the first telecobalt beam therapy unit was installed and represented a further improvement in the treatment facilities with its skin and bone sparing effect. The use of wedge filters in conjunction with cobalt therapy has, in some instances, enabled a greater localization of maximum irradiation to the tumor-bearing area (Fig. 6).

More recently other sources of irradiation have become available, both for external and interstitial therapy, which have economic and certain physical characteristics of advantage in the treatment of lesions at specific sites. Reference is made particularly to such sources as cesium 137, cobalt 60, gold 198, yttrium 90, iridium 192, and tantalum 182. This latter isotope, in the form of wire, is being used quite extensively in our clinic as a substitute for radium, and we believe that it has certain definite advantages over the latter for some lesions involving the floor of the mouth, base of the tongue, and the buccal mucosa. Tantalum wire is highly malleable and

ductile, so that the wires are easily cut to the exact length and bent to any desired shape. In order to obtain a uniform radiation field two strengths of wire are available, one having about twice the linear intensity of the other. The wire is surrounded by 0.1 mm. platinum sheath to absorb the beta particles (Fig. 7, *A-D*).

No attempt has been made in this study to go into all the intricacies of the wide variety of treatment methods and techniques. However, in reviewing the cases of the early period, one cannot help but be impressed with the clinical judgment and observation of the clinicians of those days who did not have accurate dosage tables, such as those of Quimby, Paterson and Parker, and Strandquist for their guidance. Calculation of the dosages then employed, particularly of implants, fall very well within the standard dosage tables currently in use.

At the present time, small localized lesions without lymph node involvement may be treated by radium implant or mold only (Fig. 8, *A-C*). However, the majority of cases receives external irradiation, usually by means of cobalt 60 teletherapy, with or without wedge filters, and including

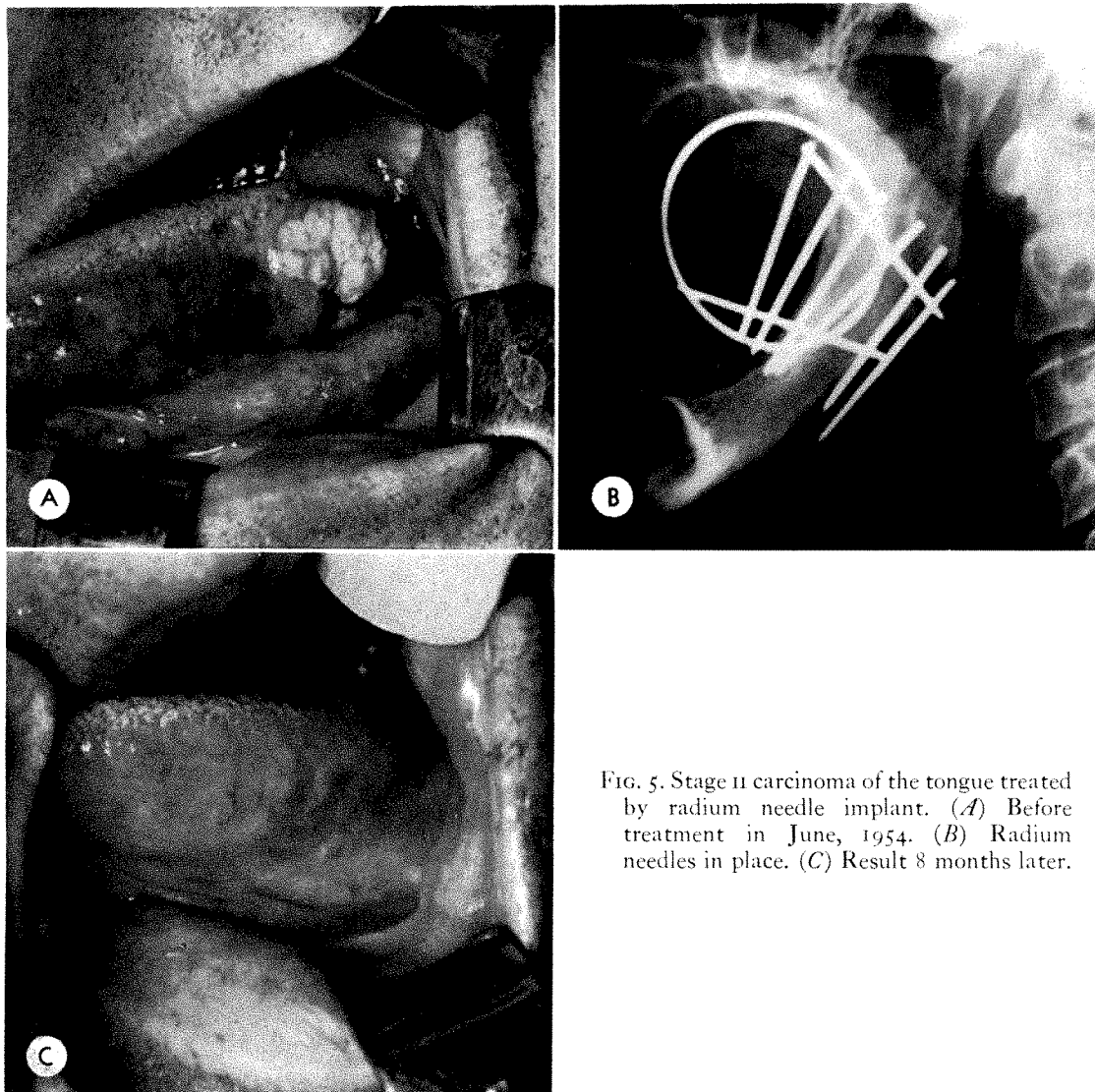


FIG. 5. Stage II carcinoma of the tongue treated by radium needle implant. (A) Before treatment in June, 1954. (B) Radium needles in place. (C) Result 8 months later.

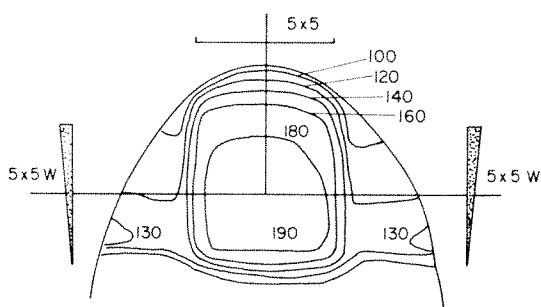


FIG. 6. Dose distribution in case of carcinoma of the floor of the mouth treated with an anterior field and two parallel lateral fields, using wedge filters.

not only the primary site, but also the adjacent lymph node areas. This may be the sole method of treatment but, where possible, it is combined with an interstitial implant, in which case about half the tumor dose is given by each. The dose for implants is usually administered at the rate of 1,000 r per day, while that for the external irradiation is planned at 1,200 to 1,500 r per week.

TREATMENT RESULTS

In Table XI, an assessment of the control of the primary lesion by initial treat-

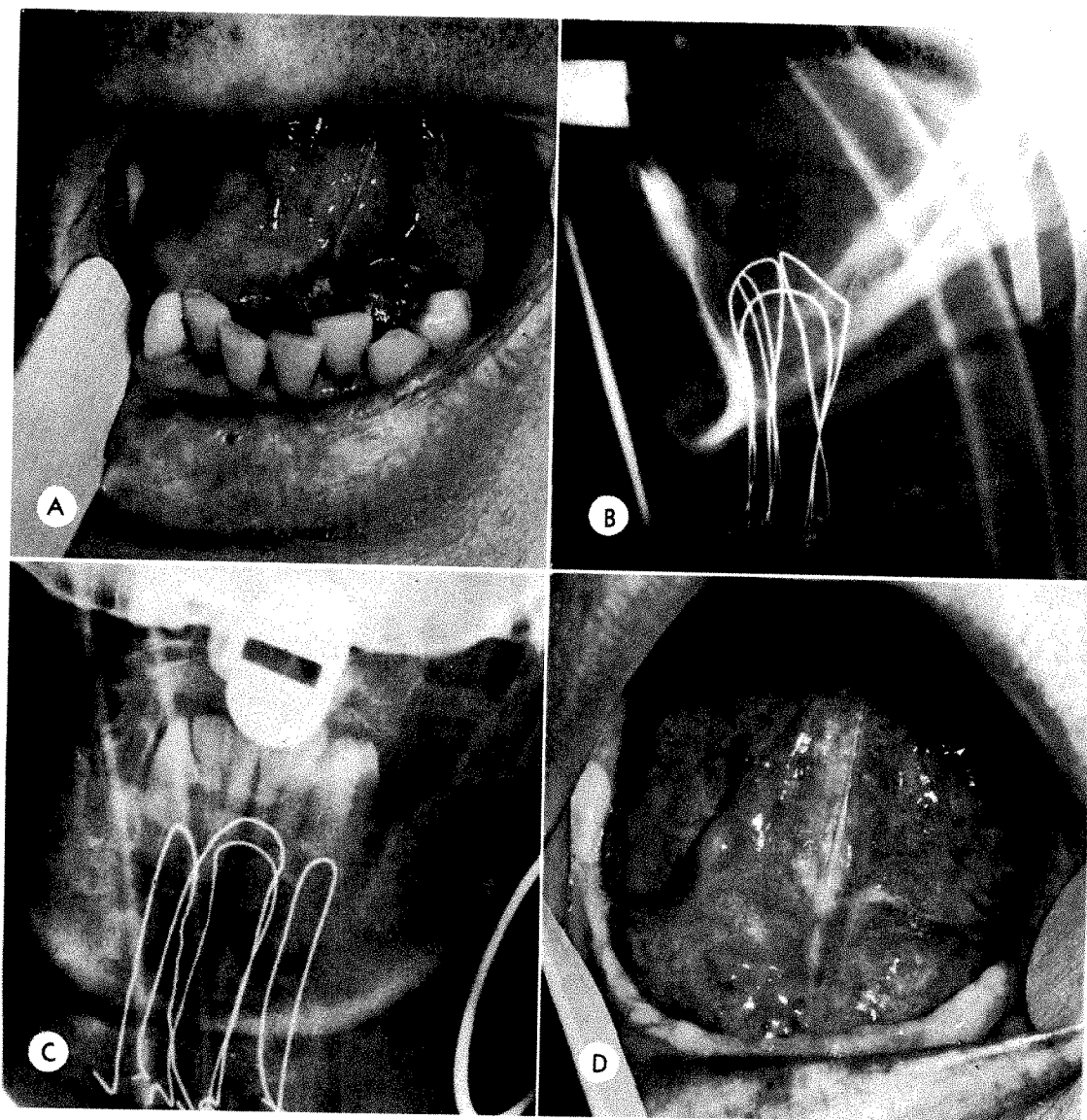


FIG. 7. Carcinoma of the floor of the mouth. (A) Pretreatment. (B and C) Tantalum wire volume implant, 3,000 r in 28 hours. The patient also had Co^{60} external therapy, 3,500 r in 4 weeks. (D) Five months post treatment.

ment is recorded. By "initial" treatment is meant that which has been accomplished within three months. The term "controlled" indicates that the primary lesion remained healed for five years, or until the death of the patient. In other words, the primary lesion no longer presented a problem during the patient's life time or for the five year period. Even in those cases in which initial treatment had not been successful, subsequent treatment still afforded

a reasonable chance of control (Table XII).

Table XIII shows the total control of the primary lesion in the entire series. This has been accomplished mainly by radiotherapy, but in some instances was combined with surgical methods. The role that surgery played in the management of the primary lesion is shown in Table XIV and was employed in 239 cases.

The distribution and control of the treated primary lesions of the tongue, ex-

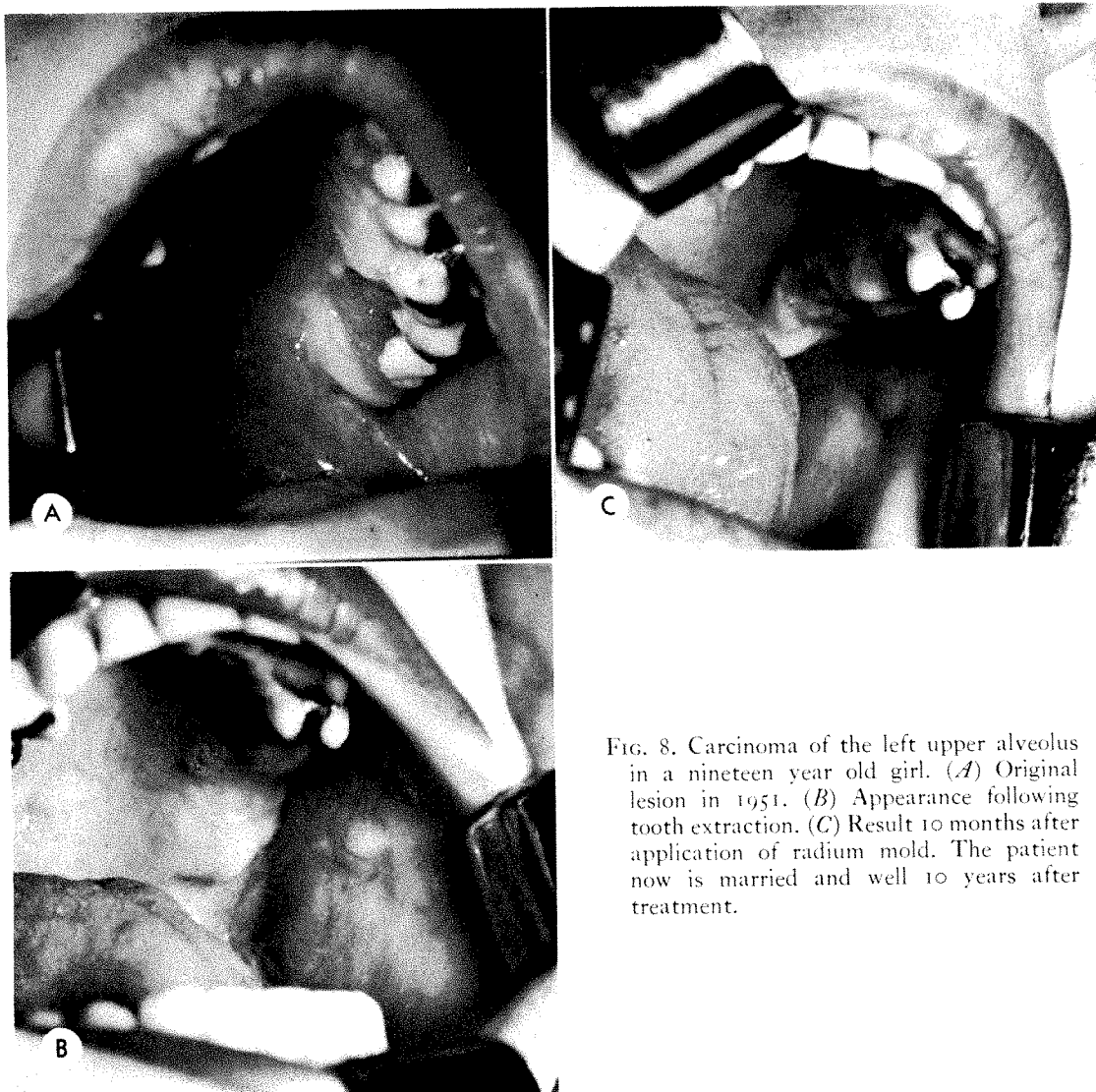


FIG. 8. Carcinoma of the left upper alveolus in a nineteen year old girl. (A) Original lesion in 1951. (B) Appearance following tooth extraction. (C) Result 10 months after application of radium mold. The patient now is married and well 10 years after treatment.

TABLE XI

CONTROL OF PRIMARY LESION BY INITIAL TREATMENT

Site	Early Cases		Late Cases	
	No. of Cases	Per Cent Controlled	No. of Cases	Per Cent Controlled
Tongue	395	49.9	348	23.6
Buccal mucosa	223	52.5	175	24.6
Gingiva	164	47.0	256	26.2
Floor of mouth	116	61.2	97	34.0
Palate	61	54.1	69	30.4
All cases	959	51.6	945	26.0

TABLE XII

CONTROL OF PRIMARY LESION BY
SUBSEQUENT TREATMENT

Site	Early Cases		Late Cases	
	No. of Cases	Per Cent Controlled	No. of Cases	Per Cent Controlled
Tongue	148	53.4	117	24.8
Buccal mucosa	85	43.5	67	25.4
Gingiva	66	42.4	116	37.1
Floor of mouth	35	68.6	30	36.7
Palate	24	33.3	30	26.7
All cases	358	49.2	360	30.0

TABLE XIII

TOTAL CONTROL OF PRIMARY LESION IN 1,929 CASES

Site	Per Cent Controlled		
	Early	Late	Total
Tongue	69.9	31.9	52.1
Buccal mucosa	69.0	34.3	53.7
Gingiva	64.0	43.0	51.1
Floor of mouth	81.9	46.4	65.8
Palate	67.2	42.0	53.0
All cases	70.0	37.5	53.8

TABLE XIV

ORAL CARCINOMA, 1929-1958
SURGICAL TREATMENT OF PRIMARY LESION

Site	No. of Cases	In Initial Treatment		In Subsequent Treatment	
		No.	Per Cent	No.	Per Cent
Tongue	763	14	1.8	60	7.9
Buccal mucosa	406	10	2.5	33	8.1
Gingiva	423	24	5.7	57	13.5
Floor of mouth	219	6	2.7	23	10.5
Palate	133	6	4.5	6	4.5
Total	1,944	60	3.1	179	9.2

TABLE XV

RECORDED INVOLVEMENT OF LYMPH NODES

Site	Cases	Per Cent with Nodes Involved		
		On Admission	Later	At Any Time
Tongue	763	33.5	29.4	63.2
Buccal mucosa	406	25.9	15.8	41.4
Gingiva	423	33.6	17.3	51.1
Floor of mouth	219	35.2	23.7	58.5
Palate	133	26.3	21.8	48.1
Total	1,944	31.6	22.8	54.5

TABLE XVI

ORAL CARCINOMA, 1929-1955
CRUDE FIVE YEAR SURVIVAL RATES BY LYMPH
NODE INVOLVEMENT ON ADMISSION

Site	No. of Cases	Per Cent Survival	
		Nodes Not Involved	Nodes Involved
Tongue	686	35.2	15.5
Buccal mucosa	374	40.4	12.9
Gingiva	387	40.9	22.2
Floor of mouth	183	49.5	22.5
Palate	118	30.4	11.5
Total	1,748	39.9	21.1

TABLE XVII

ORAL CARCINOMA, 1929-1958
CONTROL OF NECK NODES BY SURGICAL TREATMENT
(WITH OR WITHOUT RADIOTHERAPY)

Site	Nodes Involved			
	On Admission		Later	
	No. of Cases	Per Cent Controlled	No. of Cases	Per Cent Controlled
Tongue	100	31.0	146	42.5
Buccal mucosa	31	41.9	45	40.0
Gingiva	48	37.5	32	53.1
Floor of mouth	24	62.5	32	62.5
Palate	6	—	18	83.3
Total	209	37.3	273	48.4

cluding 13 involving the whole tongue and 5 cases with the site not stated, are graphically illustrated in Figure 9. Space does not permit showing the distribution of lesions for all sites. With the possible exception of carcinoma of the palate, the right side of the mouth was involved as often as the left. In the palate cases it was in the ratio of 4:5. The lower gingivae were involved two and a half times as frequently as the upper. Lesions of the buccal mucosa occurred just over twice as often in the lower as the upper half.

TABLE XVIII
PATIENTS RECEIVING SURGICAL TREATMENT

Site	Total Cases	No. Treated Surgically*	Type of Operation		
			Local Excision	Block Dissection	Other (Major)
Tongue	763	281	53	205	23
Buccal mucosa	406	98	25	61	12
Gingiva	423	127	26	51	50
Floor of mouth	219	68	12	38	18
Palate	133	36	8	24	4
All cases	1,944	610	124	379	107

* With or without radiotherapy.

The adverse influence that lymph node involvement has on survival rates is well known and is demonstrated in the following tables. The incidence of lymph nodes in this series is shown in Table xv, with the highest incidence present in carcinomas of the tongue, and the lowest in buccal mucosal lesions. Table xvi shows that with lymph node involvement on admission, the chances of survival are reduced by between 50 per cent and 65 per cent.

The success of the surgical treatment of the neck nodes is shown in Table xvii. It is interesting to note here that nodes developing later during the period of follow-up showed a higher proportion controlled than did those that were present on admission. This likely indicates that they were discovered at an earlier stage in their development because of the close follow-up policy.

Finally, Table xviii shows the total number of surgical procedures recorded that have been carried out on this entire series.

DISCUSSION

At the present time, the only way we have of assessing the effectiveness of treatment is by retrospective studies using, for example, the five year survival.

The possibility of predicting survival rates on the basis of limited past experience, as suggested by Boag, is intriguing. This is the use of the maximum likelihood

method to estimate or predict survival rate. To evaluate the method, we have punched on cards all the basic data of 35,000 cancer patients who have been registered at our clinic. Any group of these patient records may be used to make a survival table. It is possible, for instance, to take the patients treated for cancer of the tongue from 1940 to 1944 and determine how the record will appear on, say, January 1, 1945, or any other date desired.

The survival curve forms the starting point for the prediction calculations which have been of several types. The whole procedure is quite workable because the calculations are carried out by an electric com-

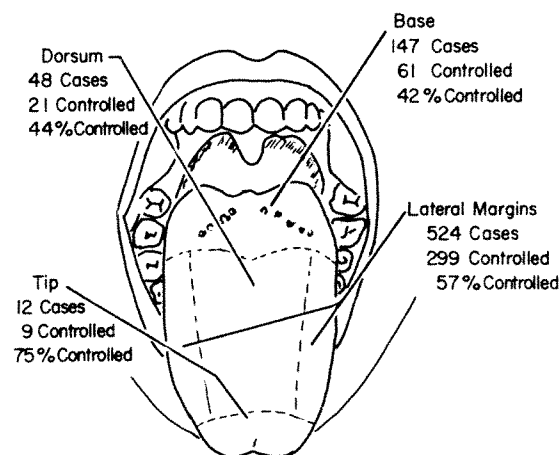


FIG. 9. Result of treatment in 731 cases of cancer of the tongue based on location of the primary lesion.

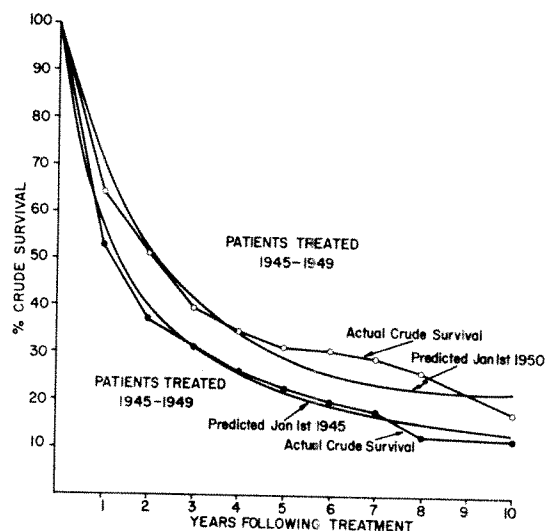


FIG. 10. Percentage crude survival curves of all patients treated between 1945 and 1949.

puter (IBM 650) and require only a few minutes to complete.

In Table XIX and Figure 10 a typical application of the technique for lesions of the tongue is given. The five-year survival predictions were made just five years after treating the first patient. The agreement between the predicted and actual crude five year survivals obtained five years later is, in general, very good. This has also proved to be the case when the method was applied to other cancer sites.

This procedure should be a real help in assessing new developments in therapy in the coming years.

TABLE XIX

COMPARISON OF PREDICTED AND ACTUAL CRUDE SURVIVAL IN LESIONS OF THE TONGUE

Patients Treated	Date of Analysis	No. of Patients	Predicted Crude Survival	Actual Crude Survival
1929-34	Jan. 1935	101	21.1%	26.4%
1935-39	Jan. 1940	88	30.5%	32.7%
1940-44	Jan. 1945	141	21.8%	22.9%
1945-49	Jan. 1950	146	29.0%	31.5%
1950-54	Jan. 1955	162	28.0%	28.9%
1955-59	Jan. 1960	157	34.3%	—

CONCLUSION

A plea is made for continuing close co-operation between the various specialties dealing with malignant disease. In the case of intra-oral cancer it is believed that surgery and radiotherapy will continue to play the major part in the management of these lesions for a number of years to come in spite of those who believe that a miracle drug or cure is just around the corner. Even in the event that such a cure becomes available, one would still feel that surgery and radiotherapy would probably continue to be the treatment of choice for the earlier lesions at least, and such cure reserved for failures or for the more advanced cases.

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NECROSIS IN TREATMENT OF INTRAORAL CANCER BY RADIATION THERAPY*

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THE use of radiation therapy in treatment of patients with intraoral cancer will result in some degree of necrosis in a certain percentage of cases. Some radiation therapists are unwilling to accept the responsibility for the care of the necrotic ulcers when they do arise, and so may be reluctant to administer a full tumor dose of radiation therapy to cancers of the intraoral cavity, particularly those approximating bone. If the therapist himself does not feel qualified to care for the patients presenting radiation necrosis, he should have a surgical colleague ready to accept the responsibility and care of the patient when and if this complication arises.

The management of many of these cancers is best carried out by means of a volume implant with radium needles of low intensity. The insertion of these needles should be accomplished by a competent therapist of experience with an adequate knowledge of the physics of radiation. Following delivery of a full tumor dose of radiation to any given intraoral cancer, either by interstitial or by external radiation, the possibility of the development of necrosis must be recognized and proper treatment administered on its initial appearance. Necrosis may appear within two to three months following completion of therapy or at any time thereafter. The dangers of attempting to re-irradiate tissues previously irradiated are apparent. To undertake such a task results in not only failure to control the cancer but also in the development of necrosis.

The first effects of radiation by radium or roentgen ray on human tissues are hyperemia and edema. Fibrosis and telangiectasia of skin and mucous membranes do

not begin to develop until several weeks to months later. Necrotic ulcers may present without a known initiating factor but usually some small trauma has been the true cause of the beginning breakdown of tissue.

The best treatment of radiation necrosis is prophylactic. Therapy carefully administered should produce necrosis in a minimal number of cases. Certainly no radiation of any kind should be given in a field previously irradiated. Therefore, once a course of radiation therapy has been started, it should be carried out to completion without interruption until the full tumor dose desired has been administered.

The edentulous patient has a better chance of avoiding necrosis than one with teeth. Since radiation therapy was first used in the treatment of cancer of the intraoral cavity, the care of the teeth has been a pertinent and debatable question. Should all teeth in the field to be irradiated be extracted? The consensus now seems to be that any teeth should be extracted which might need removal within the next twelve months. All others should be carefully cleaned. The patient must be given careful instructions as to the importance of good oral hygiene, during and after the completion of this course of radiation therapy. Frequent irrigations with warm salt and soda solutions are conducive to cleanliness and also to his comfort. The use of sodium perborate as a tooth powder is also of value in promoting good oral hygiene. Only the mildest of narcotics should be permitted and the use of mouth washes containing cocaine or its derivatives should be condemned.

Following the completion of irradiation

* From The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.
Presented at the Forty-third Annual Meeting of the American Radium Society, Colorado Springs, Colorado, May 11-13, 1961.

and after subsidence of the reaction, the routine for intraoral care, established during the course of therapy should be continued. Patients who have been treated by irradiation for lesions of the intraoral cavity, pharynx or larynx should not be permitted to smoke. Irradiated mucous membranes after the subsidence of the radiation reaction are devoid of their normal protection of mucus. Smoking tends to dry still more these mucous membranes, producing a more fertile field for the introduction of infection, subsequent to even the slightest trauma. Sharp jagged edges of teeth frequently initiate the process. Partaking of foods at temperatures too hot for even normal mucous membranes is a habit prevalent among civilized peoples. Coffee, tea and soup are the most common offenders in initiating necrosis.

The development of a necrotic ulcer in the site of the primary irradiation soon after the performance of a radical neck dissection for management of metastatic cervical cancer has been observed, particularly if the operative procedure is done within three weeks following irradiation of the primary tumor. Interference with the blood and lymph supply to the region of the primary tumor seems to augment, if not actually to initiate, the production of necrosis at times.

The patient in whom necrosis develops suddenly notices a small painful ulcer which enlarges rapidly. The irradiated edematous and fibrotic tissues with, by that time, a decreased blood supply are unable to combat the local invasion of organisms. The presence of the saprophytes, native to the normal saliva, tends to produce a rapid extension of the necrotic process throughout the irradiated area.

Any active treatment should be conservative. All necrotic ulcers heal slowly and the exact situation should be explained early to the patient, particularly in regard to the long morbidity. With conservative treatment, the chance of obtaining a better functional and cosmetic result are far greater than with more radical measures.

These procedures should be avoided until all conservative means fail.

The early or superficial area of necrosis should be treated by careful sprays and irrigations with warm mild solutions, preferably salt and soda. Zinc peroxide powder mixed with 1/6 per cent carboxymethylcellulose in hydrogen peroxide to form a moderately thick paste has been found to be the most suitable medication in controlling the spread of the necrosis. Liberation of oxygen from this zinc peroxide paste destroys the saprophytes and prevents the spread of the necrosis. Later, this medication promotes healing in irradiated membranes. Gauze of suitable size, soaked in this paste, should be kept in contact with the ulcer constantly. Dressings should be changed every three to four hours. If left in place too long, they harden and become uncomfortable to the patient. The potency of the paste is attenuated in three to four hours. If the replacement of the zinc peroxide dressing is not feasible during the night hours, gauze saturated with 5 per cent neomycin solution has been found to be fairly satisfactory. For those patients who are unable to tolerate the zinc peroxide paste because of the burning sensation caused by the hydrogen peroxide carrier, neohydeltrasol 0.5 per cent has been found to be a good substitute. This solution, a neomycin-cortisone preparation, should be used as a topical spray.

Necrotic tissue should be cut away from the edges of the ulcer whenever necessary and feasible. The possibility of active bleeding at any time must be kept in mind. Ligation of afferent arteries should be done only when active hemorrhage seems to be imminent. Reducing the blood supply has been found to increase the spread of the necrosis. When all necrotic tissues have been removed, dressings of gauze saturated with acriflavine have been found to be advantageous in promoting healing.

With the involvement of the mandible, pain may develop to such a degree that alcohol block of the mandibular branch of the trigeminal nerve becomes mandatory.

In many instances a partial resection of the jaw is indicated. Infrequently is complete resection of the mandible necessary. Removal of any portion of a jaw in such instances is best accomplished by the intraoral route. Following section of the horizontal ramus of the mandible at a chosen point, dissection is carried backward and upward toward the temporomandibular joint where disarticulation completes the procedure. The operation should be preceded by a tracheostomy. The postoperative care of the patient is much more satisfactory if this minor procedure is performed, and postoperative complications such as obstruction to the air passages and pneumonia are minimized. A feeding tube is inserted through the nose, either at the time of operation or as soon as the patient is conscious. The operative site is packed with gauze soaked in 2 per cent neomycin and kept in place for three to four days. Subsequent packings are changed twice daily. Preferably, zinc peroxide paste is used during the day and neomycin at night. Mouth irrigations are continued by the patients. Within a week to ten days the patient himself should be able to change the packing with less discomfort than when done by another person. Pain which up to time of operative removal has usually been severe is found to be minimal soon after the removal of the mandible, and the use of narcotics may soon be unnecessary. Healing will be complete in about three weeks. The last area to heal will be the cut end of bone in the anterior border of the wound. Sequestration of small fragments of bone may continue here for several weeks. Rarely does a draining point develop in the submaxillary region from osteomyelitis in those patients in whom resection of the jaw has not been too long delayed and in whom the operative approach has been through the intraoral cavity, rather than through the submaxillary triangle. Following a partial resection of the jaw, operative defect is minimal and the cosmetic appearance but little impaired. Attempts to replace resected bone by means of grafts or prosthesis

have not been successful. Irradiated tissues do not take kindly to the insertion of foreign substances as prosthetic appliances and such attempts have now been abandoned. The patient soon adapts himself to a soft diet and accepts without complaint the inability to wear a lower denture.

If untreated, pain from necrotic ulcers soon becomes unbearable. With the increasingly offensive odor, ingestion of food becomes difficult and the patient is rapidly reduced to a state of debility and inanition.

INCIDENCE

At M. D. Anderson Hospital during the past nine years (1952-1959, inclusive), 441 patients have been treated for cancer of the intraoral cavity. In the tables, the anatomic sites are listed as follows: tongue, floor of mouth, gum and buccal mucosa. The individual number of patients is listed for each site. Those treated before and after admission to M. D. Anderson Hospital have been listed separately. The number of patients in whom necrosis developed has been tabulated for each group, and in each case the degree or stage of necrosis has been classified. If the necrosis was minimal and healing occurred in from one to three months, the necrosis has been classified as superficial; if more extensive and healing resulted in three to six months, it was classified as moderately advanced; and if still more extensive and healing was delayed for six months to a year or longer, it was classified as advanced. If bone was exposed, resulting in spontaneous or fragmented sequestration, it was also classified as advanced; the final staging was the extensive bone involvement requiring resection of some portion of the jaw and was designated as very advanced. Deaths from hemorrhage have occurred but were found to be from extension of recurrent cancer into major blood vessels, although probably the condition was augmented by the simultaneous occurrence of the necrosis. Only one fatality resulted from extension of necrosis into major blood vessels with uncontrollable bleeding.

TABLE I

SQUAMOUS CARCINOMA OF THE ORAL TONGUE
1952-1959, Inclusive

Total No. of Patients Treated	143
Previously Treated	33
Previously Untreated	110
Treated by Radiation	97
Necrosis	32
Per Cent	32.9

TABLE II

SQUAMOUS CARCINOMA OF THE ORAL TONGUE
Necrosis—32 patients of 97 treated

Healed Without Interference	4
Conservative Treatment Only	21
Sequestration of Bone or Soft Tissue Excision	4
Partial or Complete Resection of Mandible*	3
Total	32

* One patient died of necrosis.

ANALYSIS OF DATA ON NECROSIS
OF INTRAORAL CAVITY
CARCINOMA OF ORAL TONGUE

In the years 1952-1959, inclusive, 143 patients were treated for squamous carcinoma of the oral tongue. Of these, 33 had been treated before admission to M. D. Anderson Hospital. One hundred and ten were untreated previously. Of these 110 patients, 97 were treated by radiation therapy. Necrosis developed in 32, or 32.9 per cent (Table I). Of these 32 patients 4 healed without any specific treatment, 21 healed with conservative treatment only, and 4 required sequestration of bone or excision of necrotic soft tissues. In 3 patients partial resection of the mandible was necessary. One of these patients died of hemorrhage as the result of extending necrosis (Table II).

The type of radiation therapy used in the 32 patients is shown in Table III. Of the 4 patients in whom healing resulted without any specific type of treatment, 2 received interstitial therapy, 1 external radiation, and 1 combined therapy. Of the 21 treated

conservatively, 13 received interstitial radiation, 2 external radiation and 6 a combination of both external and interstitial radiation. Of the 4 patients requiring sequestration of bone, 3 received interstitial radiation and 1 both external and interstitial therapy. The 3 patients requiring resection of the mandible, of whom 1 died of hemorrhage, were treated by a combined external and interstitial radiation.

Table IV shows the average elapsed time following irradiation before the development of necrosis according to the type of radiation used. In 7 patients, necrosis developed in the interval of one to three months; 6 of these received interstitial and 1 external radiation. In 9 patients necrosis appeared in three to six months. Four of these received interstitial, 1 external, and 4 combined external and interstitial radiation. In 7 patients necrosis developed in six months to one year. Four of these received interstitial radiation, 1 external and 2 combined radiation therapy. Necrosis did not develop in 9 cases until the lapse of one

TABLE III

NECROSIS IN 32 PREVIOUSLY UNTREATED CASES OF CARCINOMA OF THE ORAL TONGUE
Treatment According to Type of Radiation

Type of Therapy	Healed without Treatment	Conservative Treatment	Sequestration of Bone	Resection of Mandible	Total
Interstitial	2	13	3	1	19
External	1	2	0	0	3
Interstitial and External	1	6	1	2	10
Total	4	21	4	3*	32

* One died as result of necrosis.

TABLE IV

NECROSIS IN 32 PREVIOUSLY UNTREATED CASES
OF CARCINOMA OF THE ORAL TONGUE

Time of Appearance of Necrosis
Following Irradiation

Type of Therapy	1-3 mo.	3-6 mo.	6 mo. to 1 yr.	Longer than 1 yr.	Total
Interstitial	6	4	4	7	21
External	1	1	1	0	3
Interstitial and External	0	4	2	2	8
Total	7	9	7	9	32

year. Seven of these patients received interstitial therapy and 2 combined external and interstitial radiation.

CARCINOMA OF THE FLOOR OF THE MOUTH

Ninety-nine patients were treated for squamous carcinoma of the floor of the mouth at M. D. Anderson Hospital from 1952-1959, inclusive. Of these, 17 had been treated previously. Of the 82 untreated, 69 received radiation therapy and 39, or 56.5 per cent, developed necrosis to some degree (Table v). Of these 39 patients, none healed without interference. Twenty-two healed with conservative treatment only. Six required sequestration of bone or minor excisions of soft tissue, and 11 patients required partial resection of the mandible (Table vi).

Of the twenty-two patients who healed with conservative treatment, 11 had inter-

TABLE V

SQUAMOUS CARCINOMA OF THE FLOOR OF THE MOUTH
1952-1959, Inclusive

Total No. of Patients Treated	99
Previously Treated	17
Previously Untreated	82
Treated by Radiation	69
Necrosis	39
Per Cent	56.5

TABLE VI

SQUAMOUS CARCINOMA OF THE FLOOR OF THE MOUTH
Necrosis—39 Patients of 69 Treated

Healed without Interference	0
Conservative Treatment Only	22
Sequestration of Bone or Soft Tissue Excision	6
Partial or Complete Resection of Mandible	11
Total	39

stitial therapy, 1 had external therapy, 7 had interstitial and external therapy, and 3 had surgical treatment and radiation (Table vii). Of the 6 patients in whom sequestration of bone was necessary, 2 had interstitial therapy, and 4 interstitial and external therapy. In those cases where resection of the mandible was necessary, 2 had interstitial therapy, 3 had external therapy, 5 interstitial and external therapy, and 1 radiation and surgery. Reading across, Table vii shows that 15 patients of the group of 39 developed necrosis following interstitial therapy, 4 after external ther-

TABLE VII

NECROSIS IN 39 PREVIOUSLY UNTREATED CASES OF CARCINOMA OF THE FLOOR OF THE MOUTH

Treatment According to Type of Radiation

Type of Therapy	Healed without Treatment	Conservative Treatment	Sequestration of Bone	Resection of Mandible	Total
Interstitial	0	11	2	2	15
External	0	1	0	3	4
Interstitial and External	0	7	4	5	16
Surgery and Radiation	0	3	0	1	4
Total	0	22	6	11	39

TABLE VIII

NECROSIS IN 39 PREVIOUSLY UNTREATED CASES OF
CARCINOMA OF THE FLOOR OF THE MOUTH

Type of Therapy	Time of Appearance of Necrosis Following Irradiation				Total
	1-3 mo.	3-6 mo.	6 mo. to 1 yr.	Longer than 1 yr.	
Interstitial	4	6	4	1	15
External	1	0	1	2	4
Interstitial and External	1	7	5	3	16
Surgery and Radiation	2	1	0	1	4
Total	8	14	10	7	39

apy, 16 after combined radiation therapy and 4 after radiation and surgery.

Table VIII shows the time interval in the development of necrosis in the 39 patients. In 8, necrosis occurred in one to three months after treatment, in 4 following interstitial radiation, in 1 after external radiation, in 1 after interstitial and external radiation, and in 2 following surgery and radiation. In 14 patients necrosis developed from three to six months following treatment, in 6 after interstitial therapy, in 7 after interstitial and external radiation, and in 1 after surgery and radiation. In 10 patients necrosis appeared six months to one year after treatment, in 4 following interstitial therapy, in 1 after external radiation and in 5 after interstitial and external radiation. In 7 patients necrosis did not develop until after one year, in 1 following interstitial therapy, in 2 after external radiation, in 3 after interstitial and

TABLE IX

SQUAMOUS CARCINOMA OF THE BUCCAL MUCOSA
1952-1959, Inclusive

Total No. of Patients Treated	86
Previously Treated	21
Previously Untreated	65
Treated by Radiation	47
Necrosis	16
Per Cent	34

TABLE X

SQUAMOUS CARCINOMA OF THE BUCCAL MUCOSA

Necrosis—16 Patients of 47 Treated

Healed without Interference	1
Conservative Treatment Only	8
Sequestration of Bone or Soft Tissue Excision	4
Partial or Complete Resection of Mandible	3
Total	16

external radiation, and in 1 after surgery and radiation.

CARCINOMA OF THE BUCCAL MUCOSA

Eighty-six patients compose the group with squamous carcinoma of the buccal mucosa. Twenty-one had been treated previously; 65 were untreated before admission. Of these, 47 were treated by radiation and in 16, or 34 per cent, necrosis to some degree developed (Table IX). In 1 patient the necrosis healed without interference, 8 received conservative treatment only, 4 required sequestration of bone or soft tissue excision and in 3, partial resection of bone was necessary (Table X).

When the data are analyzed as to the type of therapy used in this group of patients, it is found that the 1 patient who healed without treatment received interstitial and external therapy. Eight patients healed after conservative treatment only, 5 having been treated by interstitial therapy, 2 by combined external and interstitial therapy and 1 by surgery and radiation. Four patients required sequestration of bone, 2 who were treated by interstitial radiation, 1 by external radiation and 1 by combined external and interstitial therapy. Three patients had resection of the mandible. Two of these patients were treated by external radiation and 1 by combined external and interstitial radiation (Table XI).

In these 16 patients, necrosis did not appear until after the lapse of one year in 7 patients, 5 having received interstitial radiation and 2 combined interstitial therapy and surgery. In 6 patients, necrosis de-

TABLE XI

NECROSIS IN 16 PREVIOUSLY UNTREATED CASES OF CARCINOMA OF THE BUCCAL MUCOSA
Treatment According to Type of Radiation

Type of Therapy	Healed without Treatment	Conservative Treatment	Sequestration of Bone	Resection of Mandible	Total
Interstitial	0	5	2	0	7
External	0	0	1	2	3
Interstitial and External	1	2	1	1	5
Surgery and Radiation	0	1	0	0	1
Total	1	8	4	3	16

veloped from six months to one year after therapy, 2 having been treated by interstitial radiation, 1 by external radiation, 2 by combined therapy and 1 by surgery and radiation. In 1 patient treated by combined radiation therapy, necrosis developed three to six months after treatment. In 2 patients who had received external radiation, necrosis developed one to three months after treatment (Table XII).

CARCINOMA OF THE LOWER GUM

In the group of 111 patients treated for squamous carcinoma of the lower gum, 35 had been treated previously and 76 were untreated. Of the 76 untreated before admission to M. D. Anderson Hospital, 38 were treated by radiation and 6, or 16.2 per cent, developed necrosis. Seventeen of

the 38 were treated by radiation only and 21 by the combined planned approach of radiation and surgery. In the group of 17 patients treated by radiation only, 1 was lost to follow-up and 3 died of disease from two to eight months after treatment (Table XIII). Of the 6 patients in whom necrosis developed, 3 healed with conservative treatment only, 1 required sequestration of bone and in 2 patients resection of the mandible was necessary (Table XIV).

In the 6 instances of necrosis resulting

TABLE XIII

SQUAMOUS CARCINOMA OF THE LOWER GUM
1952-1959, Inclusive

Total No. of Patients Treated	111
Previously Treated	35
Previously Untreated	76
Treated by Radiation*	38
Necrosis	6
Per Cent	16.2

* 17 treated by radiation only (1 lost to follow-up, 3 died of disease two to eight months after treatment), 21 treated by radiation and surgery.

TABLE XII

NECROSIS IN 16 PREVIOUSLY UNTREATED CASES OF
CARCINOMA OF THE BUCCAL MUCOSA

Time of Appearance of Necrosis
Following Irradiation

Type of Therapy	1-3 mo.	3-6 mo.	6 mo. to 1 yr.	Longer than 1 yr.	Total
Interstitial	0	0	2	5	7
External	2	0	1	0	3
Interstitial and Surgery	0	1	2	2	5
Surgery and Radiation	0	0	1	0	1
Total	2	1	6	7	16

TABLE XIV

SQUAMOUS CARCINOMA OF THE LOWER GUM
Necrosis—6 Patients of 37 Treated

Healed without Interference	0
Conservative Treatment Only	3
Sequestration of Bone or Soft Tissue Excision	1
Partial or Complete Resection of Mandible	2
Total	6

TABLE XV
NECROSIS IN 6 PREVIOUSLY UNTREATED CASES OF CARCINOMA OF THE LOWER GUM
Treatment According to Type of Radiation

Type of Treatment	Healed without Treatment	Conservative Treatment	Sequestration of Bone	Resection of Mandible	Total
Interstitial	0	1	0	0	1
External	0	1	1	2	4
Interstitial and External	0	1	0	0	1
Total	0	3	1	2	6

from radiation therapy of carcinoma of the lower gum, 1 patient had been treated by interstitial radiation, 4 by external radiation and 1 by combined radiation therapy. The one patient requiring sequestration of bone was treated by external radiation, and both of the patients having resection of the mandible had been treated by external radiation (Table xv). In 4 patients of this group necrosis developed in one to three months, in 1 following interstitial radiation and in 3 after external radiation therapy. In 1 patient, treated by combined radiation, necrosis developed in the three to six month period and in 1 following treatment by external radiation after one year (Table xvi).

CARCINOMA OF THE INTRAORAL CAVITY

Analysis of the data on necrosis of the combined anatomic sites of the tongue,

TABLE XVI

NECROSIS IN 6 PREVIOUSLY UNTREATED CASES OF CARCINOMA OF THE LOWER GUM
Time of Appearance of Necrosis Following Irradiation

Type of Therapy	1-3 mo.	3-6 mo.	6 mo. to 1 yr.	Longer than 1 yr.	Total
Interstitial	1	0		0	1
External	3	0		1	4
Interstitial and External	0	1		0	1
Total	4	1		1	6

floor of mouth, buccal mucosa and gum shows a total of 439 patients treated, 106 having been treated previous to admission and 333 who had been untreated. Of this latter group, 251 were treated by radiation, among whom 93, or 37 per cent, developed necrosis to some degree (Table xvii). Five of the 93 healed without interference, 54 healed by conservative treatment only, 15 required sequestration of bone or excision of soft tissues and in 17 instances partial or complete resection of the mandible was necessary. Complete removal of the jaw was necessary in 2 instances (Table xviii).

TABLE XVII

SQUAMOUS CARCINOMA OF THE INTRAORAL CAVITY
1952-1959, Inclusive

Total No. of Patients Treated	439
Previously Treated	106
Previously Untreated	333
Treated by Radiation	251
Necrosis	93
Per Cent	37

TABLE XVIII

SQUAMOUS CARCINOMA OF THE INTRAORAL CAVITY
1952-1959, Inclusive

Healed without Interference	5
Conservative Treatment Only	54
Sequestration of Bone or Soft Tissue Excision	15
Partial or Complete Resection of Mandible	19
Total	93

DISCUSSION

Of the 93 patients who developed necrosis, 22 were listed as early, or Stage I or II cases, while 71 were advanced, or Stage III or IV cases. Treating such lesions by radiation is hazardous and necrosis must be expected in a certain percentage in order to eradicate the disease itself. Fifty-nine, or 63 per cent of these patients, are now living and free of disease, one to eight and one-half years since they were first seen and 2 are living with disease. Thirty-two patients have expired, 16 of recurrent local disease, 6 of metastasis, 6 of intercurrent disease and 4 of a second primary cancer.

Since there was only 1 mortality due to necrosis in this series of 439 patients, it is evident that the hazard of necrosis must be accepted in order to deliver an adequate dose of radiation, thereby offering the patient the best chance of cure of his disease. The morbidity of the necrosis is not to be ignored, but in the end the chances of a patient surviving, free of disease, are better than if less than a full tumor dose of radiation had been administered.

Of this group of patients treated for squamous carcinoma of the intraoral cavity, the largest number of necrosis occurred in the floor of the mouth group; namely, 39 of the 69 previously untreated patients. Further analysis of this group seemed essential to determine the incidence of necrosis in relation to the involvement of the mandible by disease at the time of admission and also to the presence of the teeth at the time of administration of radiation therapy. It was found that 8, or 20.5 per cent, showed exposure and invasion of the bone by the primary carcinoma. Of the 8, 3 presented with teeth; 5 were edentulous. The remaining 31 patients, or 79.5 per cent, revealed no evidence of invasion of the bone by the primary lesion.

Thirteen of this group had two or more teeth in the field of the radiation treatments. In 3 of the patients, extraction of all remaining teeth was carried out before administration of therapy. The remaining

18 patients with uninvolved mandible were edentulous. The presence of teeth in the radiation field is obviously an aid to the entrance of infection with subsequent development of osteomyelitis and necrosis of bone. Whether or not the teeth are extracted before radiation therapy seems in some instances to make but little difference in the end result. At present the consensus seems to be that teeth which show evidence of probable need of extraction within the ensuing year should be extracted before administration of radiation therapy whether or not they are to be included in the field of radiation.

The type of radiation therapy used in the treatment of this group of 39 patients should also be noted. Sixteen were treated by interstitial therapy only. This type of therapy consisted of implants of radium needles of low intensity in all cases except in 1 instance where gold grains (Au^{198}) were employed. One patient of this group was treated by radium implants of low intensity following failure to control the disease by surgery. Three patients received interstitial radiation supplemented by conventional external radiation therapy and 14 were treated by interstitial plus supervoltage therapy. Three patients received external therapy by supervoltage only, 1 was treated by orthovoltage external radiation only and the remaining 2 received supervoltage and orthovoltage therapy combined.

External radiation supplemental to interstitial radiation has not been used in the past two to three years when the consensus was that the possibility, if not the likelihood, of necrosis was enhanced by the combined approach. A little over a year ago, half rather than full intensity needles along the periphery of the lesion in juxtaposition to the mandible became a part of the routine plan of treatment of floor of the mouth cancer. Both these alterations seem to have decreased somewhat the incidence of necrosis, but not enough time has yet elapsed to be certain of the significance of these changes.

CONCLUSIONS

The possibility if not the likelihood of the development of necrosis in management of intraoral cancer by radiation therapy is always present if the therapist has been honest in his efforts to deliver a full tumor dose of radiation to the involved tissues. This hazard must be accepted, if patients with cancer of the oral cavity are to be treated adequately and cured. If the therapist is unwilling to accept the care and management of the necrosis when it does occur, he should have available a surgical colleague qualified to care for this complication of radiation therapy.

The incidence of radiation necrosis in treatment of patients with cancer of the intraoral cavity at M. D. Anderson Hospital during the past nine years has been charted and insofar as the records have

permitted, the extent of the necrosis has been staged and the results tabulated. Close follow-up of all patients treated for cancer of the intraoral cavity by radiation is obviously required for necrosis may develop at any time, from a few weeks following completion of therapy to the end of the patient's natural life. The dangers of attempting to re-irradiate a lesion previously treated by radiation of any kind are quite evident and should be avoided. The importance of close cooperation between the departments of radiation therapy and of surgery must be maintained in order to obtain the best treatment and end result for the patient.

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DISTANT METASTASES FROM HEAD AND NECK CANCER *

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IT IS a prevalent impression that head and neck cancer seldom extends beyond the clavicle. The unexpected appearance of distant metastases in several patients with oral cancer prompted this survey, which revealed an incidence of 21 per cent. A search of the recent literature uncovered but few reports.^{2,3,7,8}

The term "distant metastases" as employed herein refers to growths arising from but not continuous with the primary tumor. Involved lymph nodes draining the original site are not considered metastatic, but are, indeed, a part of the primary disease. Although the concept of lymph node contiguity is shared by many, others, notably Ward and Hendrick¹¹ in their excellent text, refer to the question of the draining lymph node as a separate phase of the tumor.

This report is a clinical appraisal of metastatic disease from oral cancer, not an analysis of necropsy findings such as that presented in the classic study of Willis,¹² or the review of the large number of autopsied cases by Braund and Martin.^{2,7}

Malignant tumors spread into tissue spaces from whence the tumor cells enter the lymphatics. They may enter blood vessels by direct invasion or indirectly through the minute lymphatic channels surrounding the blood vessels.^{4,5,9,10} The vertebral venous plexus, described by Batson,¹ is a significant pathway for the venous spread of tumors. The plexus extends along the entire length of the vertebral column, communicating with the sacral, lumbar, intercostal, and neck veins, and those within the skull. Neoplasms near

TABLE I
PRIMARY SITE RELATED TO THE
INCIDENCE OF METASTASES

Primary Site	No. of Cases	No. of Cases with Metastases	Per Cent
Antrum	7	2	28
Epiglottis	5	0	0
Larynx	32	4	12
Alveolar Ridge	3	1	33
Floor of the Mouth	14	5	35
Nasopharynx	18	7	39
Palate	5	1	20
Pharynx	8	2	25
Piriform Sinus	5	1	20
Tongue	24	1	4
Tonsil	11	4	36
Total	132	28	21

this complicated series of veins may invade them.

ANALYSIS OF MATERIAL

Of a total group of 132 patients observed over a five year period, 28 were found to have distant metastases, an incidence of 21 per cent.

Table I lists the anatomic sites of the original tumors and the number of metastases derived from each. It is true that the number of cases in each category is small; nevertheless, there are some trends that are worthy of emphasis. For instance, cancers arising in the floor of the mouth, nasopharynx and tonsil were more prone to disseminate to distant areas than those from the epiglottis or tongue. The tendency for

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tumors of the nasopharynx to seek bone is well recognized.

Table II and its graphic representation in Figure 1 record the primary sites of the head and neck cancers, the clinical staging, sites of distant metastatic deposits, the

time of appearance of the secondary lesions and the time of death in relation to the time of appearance of the secondary foci. It is important at this point to note that in 13 cases metastatic lesions were discovered at autopsy in addition to those

TABLE II
CLINICAL DATA IN 28 CASES OF DISTANT METASTASES FROM HEAD AND NECK CANCER

Case	Primary Site	Staging	Interval between Diagnosis and Metastasis	Location of Metastasis	Interval between Metastasis and Death	Diagnostic Method
A.A.	Tonsil	P ₃ N ₂	5 months	lung	9 days	Roentgenography; postmortem
G.F.	Tonsil	P ₁ N ₃	8 months	lung	3 months	Roentgenography
T.McG.	Tonsil	P ₁ N ₃	5 months	lung	—	Roentgenography
T.R.	Tonsil	P ₂ N ₂	12 months	lung	1 month	Roentgenography; postmortem
F.B.	Nasopharynx	P ₁ N ₃	1½ months	bone, lung	2 months	Roentgenography; postmortem
F.B.	Nasopharynx	P ₁ N ₃	8½ months	bone	—	Roentgenography
A.D.	Nasopharynx	P ₁ N ₃	12 months	lung, bone	11 months	Roentgenography
H.G.	Nasopharynx	P ₁ N ₄	3 months	bone, distant lymph node	3½ months	Roentgenography; postmortem
P.K.	Nasopharynx	P ₄ N ₂	12 months	visceral, distant lymph node	4 months	Roentgenography; postmortem
W.M.	Nasopharynx	P ₄ N ₂	7 months	bone	4 months	Surgery
S.S.	Nasopharynx	P ₃ N ₃	1 month	lung	1 year	Roentgenography
W.C.	Pharynx	P ₂ N ₃	10 months	lung, bone	6 days	Roentgenography; postmortem
R.H.	Pharynx	P ₂ N ₂	21 months	bone	3 months	Roentgenography
J.C.	Antrum	P ₃ N ₁	2 months	lung, bone	2 months	Roentgenography; postmortem
A.N.	Antrum	P ₂ N ₄	1 month	lung	—	—
A.D.	Floor of Mouth	P ₁ N ₀	9¾ years	lung, bone	3 weeks	Roentgenography; postmortem
R.B.	Floor of Mouth	P ₁ N ₂	20 months	soft tissue	8 days	Surgery; post-mortem
L.K.	Floor of Mouth	P ₁ N ₂	5 months	bone	12 months	Roentgenography; postmortem
D.M.	Floor of Mouth	P ₂ N ₂	10 months	lung	4½ months	Roentgenography
J.M.	Floor of Mouth	P ₂ N ₄	½ month	bone	5½ months	Surgery
C.H.	Larynx	P ₂ N ₄	1 month	lung	4 months	Roentgenography
W.H.	Larynx	P ₂ N ₀	24 months	lung	1 month	Roentgenography; postmortem
T.O.	Larynx	P ₃ N ₃	34 months	lung, bone	3 months	Roentgenography
J.S.	Larynx	P ₂ N ₄	0	bone	2 months	Surgery; post-mortem
G.H.	Alveolar Ridge	P ₂ N ₃	6 months	bone	2 months	Roentgenography
L.N.	Tongue	P ₁ N ₁	3 months	bone, lung	6 months	Roentgenography
P.O.	Palate	P ₃ N ₃	1½ months	bone	2 months	Roentgenography; postmortem
P.R.	Piriform Sinus	P ₁ N ₃	7 months	bone	2 years	Roentgenography

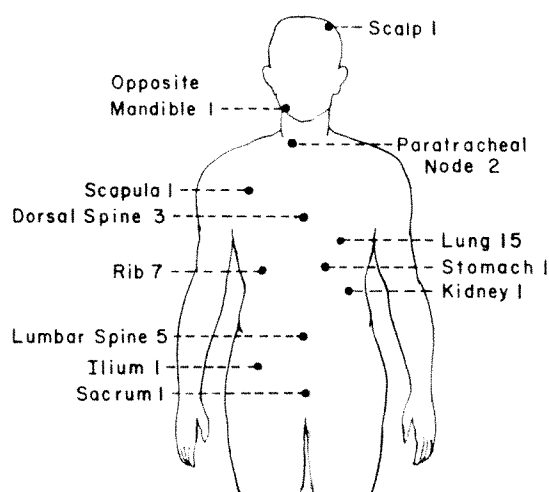


FIG. 2. An anatomic sketch showing the sites of distant metastases in the 28 cases in Table III. Bone metastases are listed on the left and soft tissue metastases on the right. The stomach and kidney lesions were diagnosed roentgenographically in the living patient.

in nature, 3 were blastic, and one area in the vertebra was mixed (Table IV).

Secondary deposits in the lung presented no distinguishing features. In all instances but one, they were multinodular without predilection for any particular lung segment. The one exception was a lymphogenous dissemination proved at post-mortem examination.



FIG. 3. Case 1. (A) Photograph showing a lesion along the floor of the mouth and frenulum and (B) a photomicrograph of the biopsy specimen, which revealed a well-differentiated squamous cell carcinoma with keratinization. (C) Chest roentgenogram showing a large lytic area in the third right rib and (D) a photomicrograph of the biopsy specimen of the rib lesion showing nests of poorly differentiated squamous cell cancer with single cell keratinization in a fairly dense fibrous stroma.

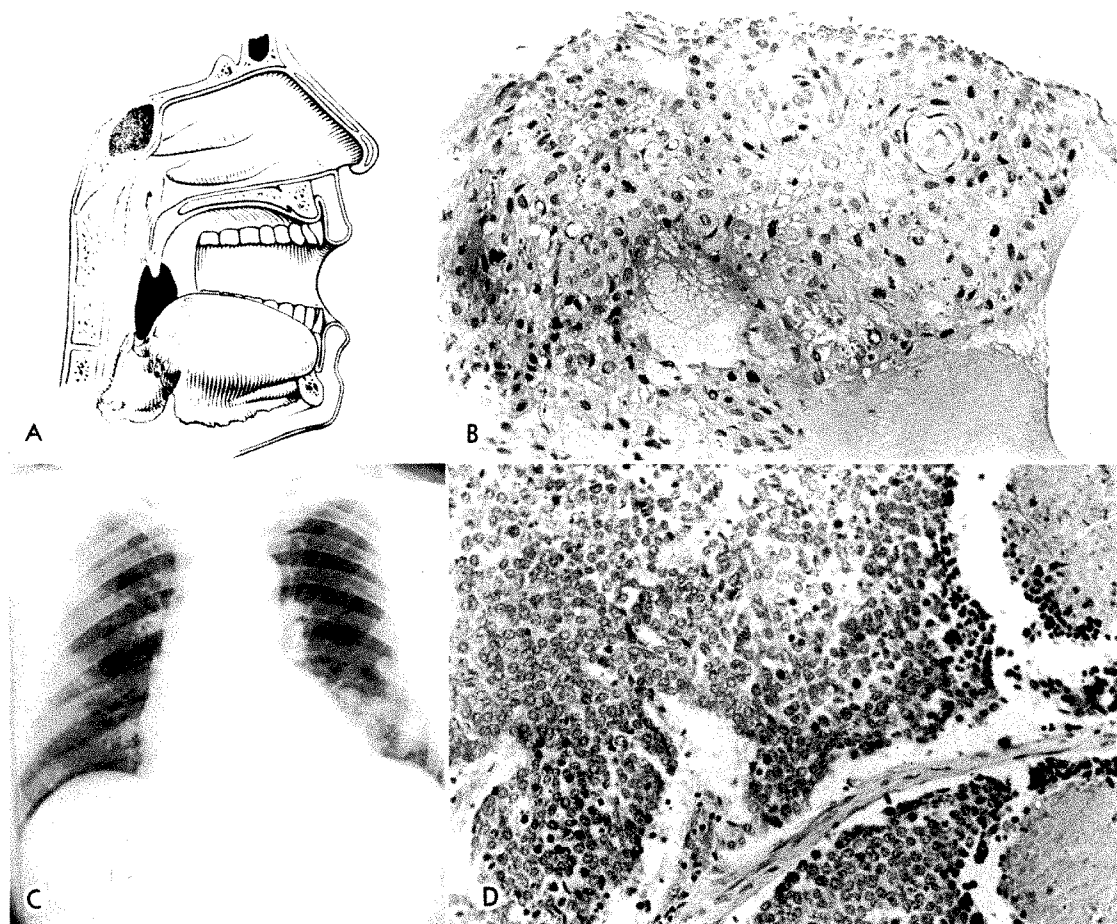


FIG. 4. Case II. (A) Diagram showing the location of a large mass in the left tonsillar fossa extending inferiorly along the lateral pharyngeal wall. (B) Microscopic study of the primary tumor demonstrating a moderately well-differentiated squamous cell carcinoma with abortive pearl formation. (C) Roentgenogram showing parenchymal nodules, especially numerous at the base of the left lung. (D) Microscopic study of a lung nodule revealing undifferentiated carcinoma with uniform cells and no evidence of keratin formation.

One nasopharyngeal tumor showed dissemination to the stomach and kidney diagnosed roentgenographically during life and proved at necropsy.

Histologically, metastatic deposits may show an increased degree of anaplasia.⁶ The metastases in 6 of the 13 cases that went to autopsy, and in 3 of 4 patients whose case histories are cited below, had this characteristic. There is a gradual loss of distinguishing features in metastatic tumors.

REPORT OF CASES

CASE I. J.M., a fifty-three year old male, had an extensive lesion along the floor of the

TABLE IV
METASTASES IN BONE

Site	No. of Cases	Lytic	Blastic	Mixed
Ribs	7	7	0	0
Lumbar Spine	5	2	2	1
Dorsal Spine	3	3	0	0
Scapula	1	1	0	0
Acetabulum	1	0	1	0
Sacrum	1	1	0	0
Opposite Mandible	1	1	0	0
Total	19	15	3	1

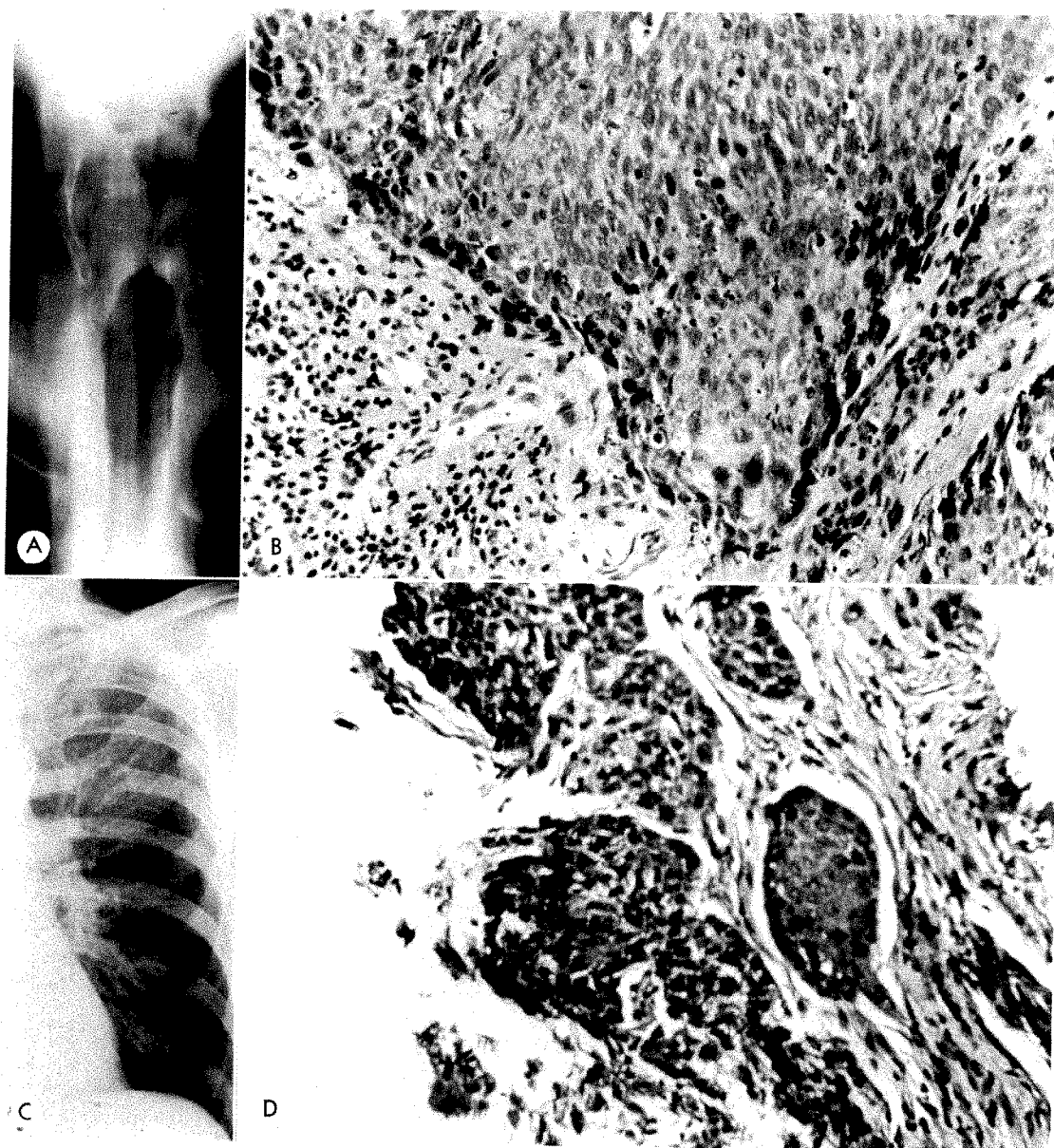


FIG. 5. Case III. (A) Roentgenogram demonstrating a large mass in the right arytenoid extending into the piriform sinus. (B) Biopsy specimen of the lesion in A shows a poorly differentiated squamous cell carcinoma with spindle shaped cells in some areas. (C) Chest roentgenogram demonstrating a large osteolytic lesion in the left sixth rib. (D) Biopsy specimen of the lesion in C shows a metastatic epithelioma comparable in histologic character to the primary tumor.

mouth and frenulum which was histologically proved to be a well-differentiated squamous cell carcinoma with keratinization (Fig. 3, A and B). A chest roentgenogram revealed a large lytic area in the third right rib (Fig. 3C). A biopsy specimen from the rib showed nests of poorly differentiated squamous cell cancer with single cell keratinization in a fairly dense fibrous stroma (Fig. 3D).

CASE II. A.A., a sixty-four year old male, was seen with a large fungating exophytic mass in the left tonsillar fossa extending inferiorly along the lateral pharyngeal wall (Fig. 4A). A massive 10×6 cm. left midjugular node was present. Roentgen therapy (with conventional energies) failed to reduce the tumor even after the delivery of a tumor dose of 7,000 r in thirty-five days. A chest roentgenogram revealed numer-

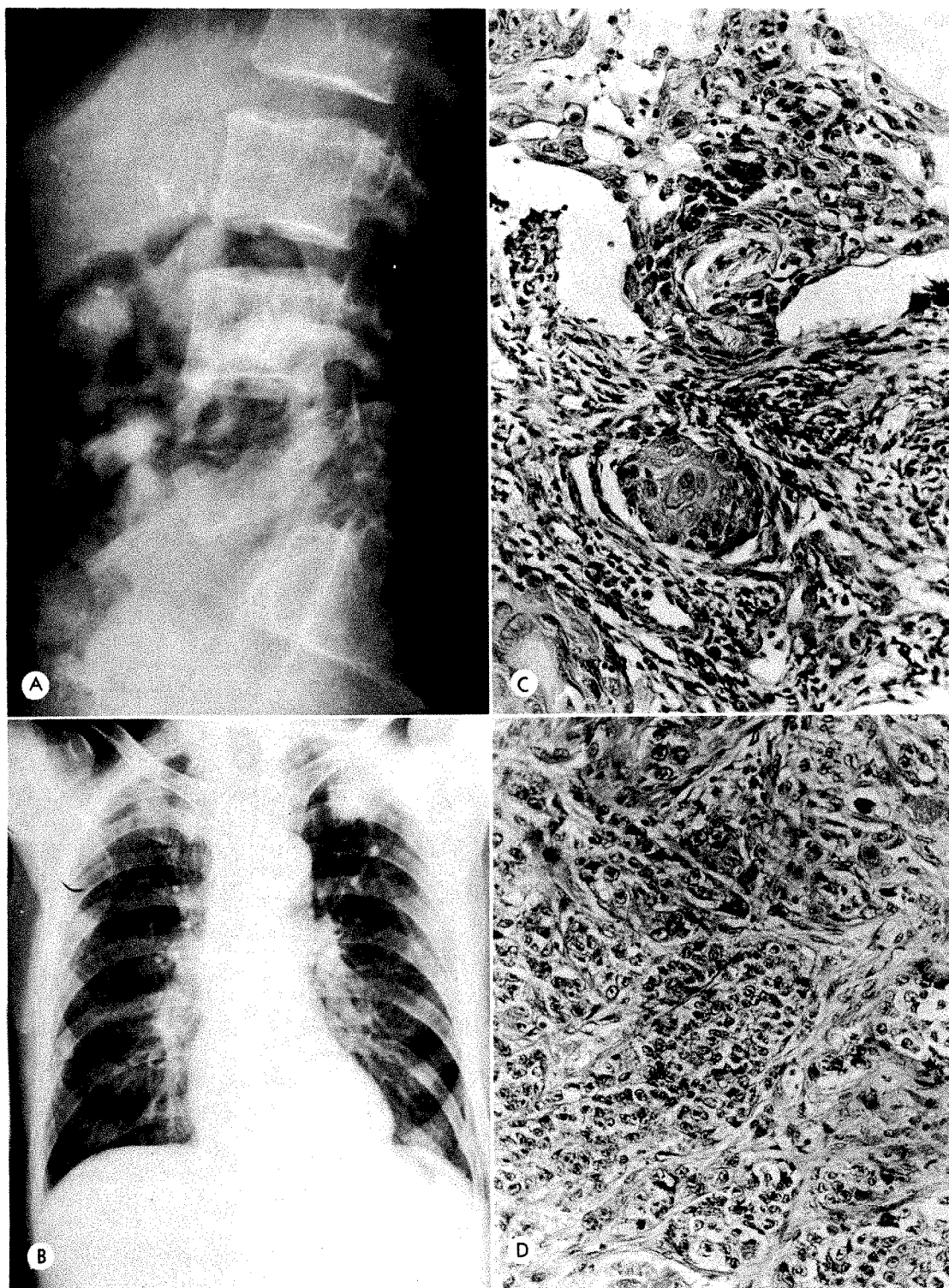


FIG. 6. Case IV. Roentgenograms demonstrating (A) an osteolytic process in L5 and (B) a pathologic fracture of the ninth right rib (arrow). (C) Microscopic study of the primary lesion shows nests of moderately differentiated squamous cells with sheets and cords of poorly differentiated cells. (D) Microscopic study of the metastatic rib lesion shows nests and cords of rather uniform but undifferentiated tumor cells with no evidence of keratinization.

ous parenchymal nodules (Fig. 4C).

Autopsy confirmed the roentgen finding. The primary tumor showed a moderately well-differentiated squamous cell carcinoma with abortive pearl formation (Fig. 4B). The lung nodules revealed completely undifferentiated cancer with uniform cells and without evidence of keratin formation (Fig. 4D).

CASE III. J.S., a fifty-one year old white male, had a large mass in the right arytenoid and extending into the piriform sinus (Fig. 5A). The cords were uninvolved. A biopsy showed a poorly differentiated squamous cell cancer with spindle shaped cells in some areas (Fig. 5B). All the lymph nodes in the right cervical chain were enlarged. A roentgenogram was taken to evaluate the sudden appearance of pain in the left chest. A large osteolytic lesion was observed in the left sixth rib (Fig. 5C). A biopsy of the rib lesion was done. This tissue revealed a metastatic epithelioma of poorly differentiated squamous cells quite comparable to the primary tumor (Fig. 5D).

CASE IV. W.C., a sixty year old male with severe dysphagia and a weight loss of 25 pounds within six months, had a large ulcerated mass in the posterior pharynx with invasion of the right palate and glossopalatine fold. Bilateral subdiaphragmatic lymphadenopathy was present. A roentgen survey disclosed an osteolytic process in L5 and a pathologic fracture of the ninth right rib in the axillary line (Fig. 6, A and B). The primary tumor had nests of moderately differentiated squamous cancer cells together with sheets and cords of poorly differentiated cells (Fig. 6C). The metastatic rib lesion showed nests and cords of fairly uniform but undifferentiated tumor cells with no evidence of keratinization (Fig. 6D).

SUMMARY

1. In a series of 132 patients with head and neck cancer, there were 28, or 21 per cent, with distant metastatic foci that were diagnosed clinically.
2. Tumors arising in the floor of the mouth, nasopharynx and tonsil were more prone to disseminate than primary tumors in the epiglottis or tongue.
3. Bones and lungs were by far the predominant sites of metastases. Bone de-

posits were principally osteolytic and lung lesions were usually nodular.

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LOCALIZATION OF BRAIN TUMORS USING RADIO- IODINATED HUMAN SERUM ALBUMIN*

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THE concept of extracranial localization of brain tumors by means of their differential uptake of gamma emitting labelled carriers is an attractive one. Brought to an efficient level, such a method would afford an excellent screening test before resort to more hazardous and onerous procedures such as pneumography or arteriography.

Presently there are two sharply demarcated techniques in the field of extracranial localization of brain tumors. These include the method proposed by Sweet and Brownell and others^{13,41,46} of coincidence counting devices on the one hand and on the other a wide variety of apparatus with which, either manually or by mechanical tracking methods, gamma emitters are used for direct detection of mass lesions by the comparison of symmetric and adjacent areas throughout the cranial vault.^{6,32,45} In this laboratory the technique involving detection of gamma emitters, such as I^{131} , was chosen deliberately over the one requiring the use of positron emitters for the following reasons: (1) the expense and rigidity in application of the arsenic method; (2) the lack of availability generally and the expense of that and other cyclotron produced isotopes; and (3) the increased toxicity and radiation hazard of arsenic over iodine.¹²

We feel that the method we have chosen deserves continuing technical development because of its safety from a public health standpoint, and its wide spectrum of usefulness in detecting intracranial space occupying lesions.

Our requirements for a good method of extracranial tumor localization include the following desiderata: (1) a reasonably high rate of detection of expanding lesions of the

cerebrum; (2) a negligible ratio of false positive results; (3) a reasonably discrete localization so that the area of suspicion can be accurately checked by specific studies such as encephalography or angiography; and (4) a sufficiently low hazard from a public health standpoint so that the tests may be repeated at frequent intervals in order to enhance their value as a screening procedure and follow-up.

The history of the use of dyes for the selective staining of the central nervous system is well documented.^{18,20,24} The method has been useful in delineating what is known about the blood brain barrier and in neuropathological studies generally.^{11,16} In 1947, Moore²⁸ reactivated interest in the field by reporting studies on the selective uptake of the dye, sodium fluorescein, by tumors of the cerebrum. This subsequently led to the tagging of the latter compound with radioactive iodine and the popularization of the method throughout the country in attempts to localize intracranial tumors using external counting devices.^{1,2,14,29}

From our present vantage point of scintillation counters, collimation devices, and improved methods for the collection of data, it is obvious that the earliest attempts at localization of brain tumors were doomed to a low level of accuracy. After Moore's description of the use of fluorescein and tagged human serum albumin, there was a period of enthusiastic investigation in many centers. Reports of the high degree of clinical localization created a climate which was somewhat detrimental to the natural development of the field. It is obvious from careful perusal of the requirements of the experimental plan that the earlier methods were grossly inaccurate.

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The conditions of the technique consisted in the need to detect a 2 cm. mass with a tumor to background ratio of 10 to 25 per cent, using uncollimated Geiger Müller detection devices. Several investigators called attention to the inherent inefficiency of the then available tools and therefore the lack of possibility of obtaining high statistical accuracy. Among these investigators were some whose observations were based on clinical data^{5,34} and others who used simulated tumors in purely physical experimental set-ups.²¹

Since Moore's original studies with diiodofluorescein, it has become apparent that the approaches to improved performance and statistical accuracy lie in two directions. The first major orientation of research is toward improved physical techniques of detection and recording. The second is the development of substances which would achieve a greater concentration in the tumor in relation to the surrounding brain.

I. PHYSICAL FACTORS AND INSTRUMENTATION

From a physical standpoint, the presenting problems are:

1. *Ratio of uptake in the normal brain to that within the lesion.* Mice with brain implants of glioma were given radioiodinated serum albumin. The tumor to normal brain ratio varied within the range of 6 to 15.³⁵ In a mock set-up with I^{131} tumor to brain ratio of 6 and tumor volume of 10 cc., the "tumor" contributes a 30 per cent increased count rate. A ratio of 4 and tumor volume of 50 cc. give essentially the same increase in count rate. Actually, the tumor frequently affords an increased count rate of only 10 to 25 per cent.

Another major difficulty is the low total activity in the brain (Table 1). The critical issue is to detect this low level activity with sufficient statistical accuracy to delineate the increase in count rate from the tumor. The statistical variation must therefore be well below 10 per cent. Since the dose to the patient should be kept low (5

TABLE I
DISTRIBUTION OF RADIOIODINATED ALBUMIN 24
HOURS AFTER INTRAVENOUS INJECTION^{33*}

Organ	Radioactivity/gm. tissue	
	Radioactivity/ml. plasma Whole Tissue	Bloodless Tissue
Brain	1.6×10^{-2}	0.5×10^{-2}
Skeletal muscle	4.4	3.3
Stomach	14.7	10.7
Liver	15.0	5.7
Pancreas	12.1	
Fat	8.4	

* Reproduced in part; courtesy of the authors.

to 7 $\mu\text{c/kg.}$), the counting time must be increased.

2. *The efficiency of detecting apparatus.* When external counters were first used to detect I^{131} tagged diiodofluorescein, spot by spot counts were taken manually positioning an end window Geiger Müller counter on corresponding points of the head consecutively. No effective collimation was used. Scintillation counters have now completely replaced Geiger Müller counters in this field (Fig. 1). These have the advantage, over and above increased sensitivity, of producing output voltages proportional to the gamma energy absorbed. With the use of pulse height analyzers (discriminators), the bias level of the primary radiation (for I^{131} , 80 per cent is 0.364 mev.) can be determined and then all energies outside this area can be eliminated (Fig. 2). This considerably reduces background and Compton scatter (which is of a lower energy), thereby increasing the sensitivity of the detecting system.¹⁹ The system is sufficiently stable only after warm-up periods of an hour or more. Changes in the supplied voltage will change the position and shape of the peak. Accordingly, a stable voltage supply and daily checks with isotope are necessary to be certain of the position of the peak.

To increase the resolution of the system, the unscattered as well as the scattered

radiation from other areas of the head (sensitive volume) must be reduced. By placing a piece of dense metal (lead, gold, or mercury) with one or more apertures in front of the crystal, collimation is obtained. The apertures may be cylindrical, conical, or hexagonal and arranged in various patterns depending upon the geometry of the lesion and the emitter used. As the degree of collimation increases, the sensitive volume of the counter decreases and the collimator becomes a better localizer.^{23,27,30} The focusing collimator (Fig. 3*A*, *a*), for example, would be able to locate the size and position of a lesion more precisely than the cone seen in Figure 3*A*, *b*. The one which most nearly satisfies the requirements for the brain scanning system is the honeycomb collimator. It focuses in a scattering medium (Fig. 3*B*) and has a very narrow sensitive radius.

An automatic device (scanner) has been developed which will carry the counters with the necessary shielding at a constant rate across the head without missing any

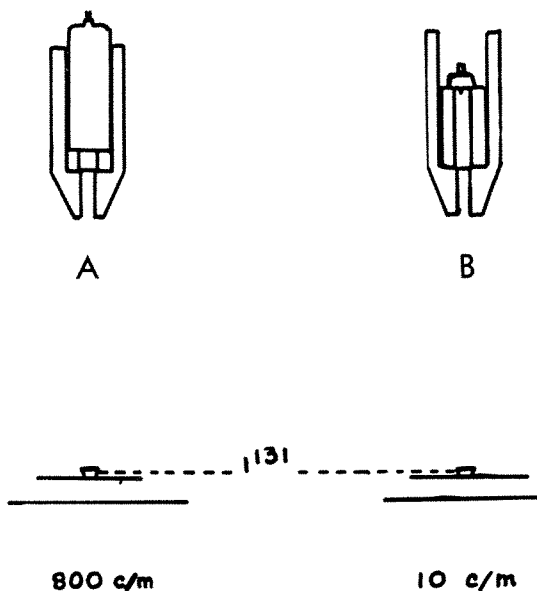


FIG. 1. Comparative sensitivity of a scintillation counter and a Geiger Müller counter at the same distance, in the same housing unit, and with the same I^{131} source. (A) Scintillation counter; $\frac{3}{4} \times \frac{3}{4}$ inch crystal with preamplifier. (B) Geiger Müller counter end window, bismuth cathode.

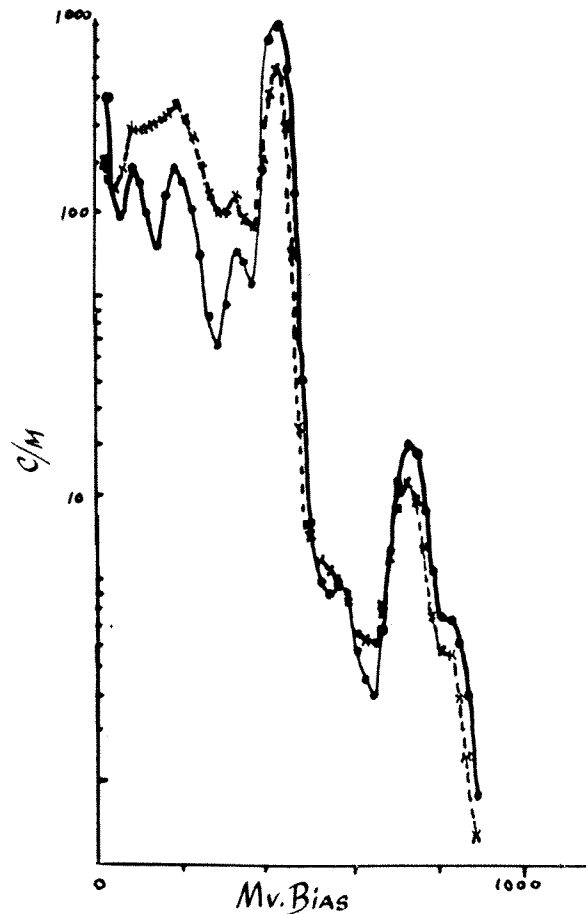


FIG. 2. I^{131} spectrum taken with a point source in air —●—, and in water —*—.

areas. The spacing between the rows can be varied as well as the rate of traverse.

Since the counts are being continuously accepted as the counters traverse the head, recording systems which also are continuous are most useful. Some of these are:

(a) Pen recorder (photoelectric) which produces a deviation of a pen in accordance with the count rate.

(b) Print-out system which follows the traverse of the scanner and makes an image after a predetermined number of counts. Included in this group are the solenoid hammer and the Teledeltos pen.

(c) Photographic recording apparatus in which pulses from a count rate meter are fed to an amplifier and then to a lamp. Although there are many variations, the maximum contrast enhancement is ob-

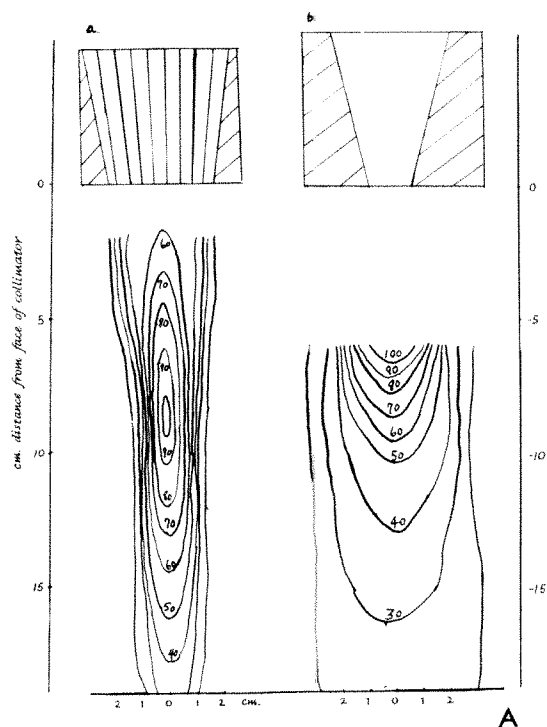


FIG. 3. (A) Isocount response to I^{131} point source in air for (a) focusing honey comb collimator and (b) cone collimator.

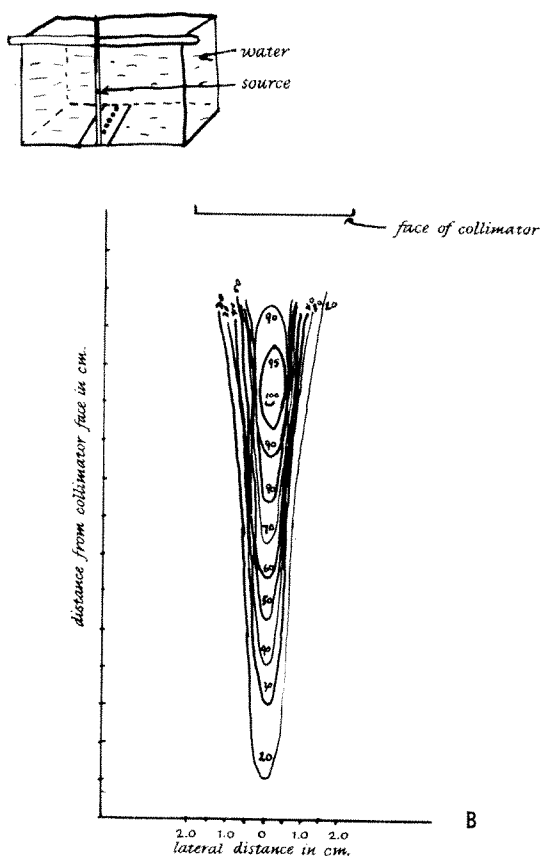


FIG. 3. (B) Isocount response with focusing honeycomb collimator and I^{131} source in water.

tained with a tungsten lamp. The contrast enhancement is especially helpful in visualization of minimum tumor uptakes. The voltage on the lamp varies directly with the count rate. With this recording method an increase in count rate of 30 per cent results in a factor of 10 increase in the brightness of the lamp, and a proportionate enhancement of the film density.^{7,8}

3. Type of apparatus used.

(1) Honeycomb collimators which focus in air at 10 cm. from the face of the collimator (Fig. 4A). The 61 holed honeycomb collimators were molded by a simple method developed by Rudolph Gand at Radiological Research Laboratory, Columbia University, and yielded precision collimators. It consists in making a shell of brass and two end plates of 1/32 inch sheet brass. Holes are drilled according to the desired layout so as to accommodate the taper pins yielding the required focus. The two end plates prevent any movement of the tapers

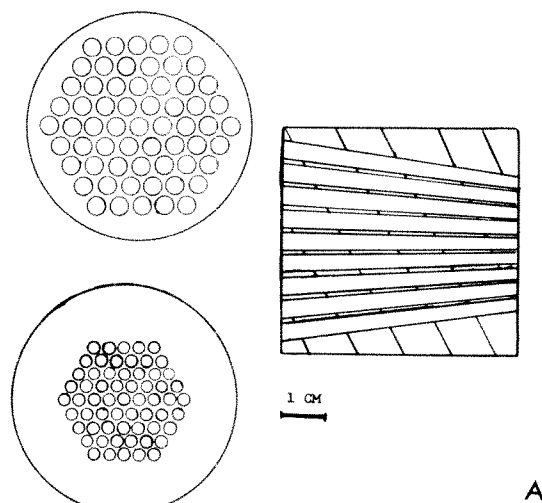


FIG. 4. (A) Focusing honeycomb collimator with 61 holes and a focus at 10 cm. from the face. Upper left: back view. Lower left: face view. Right: mid-line cross section.

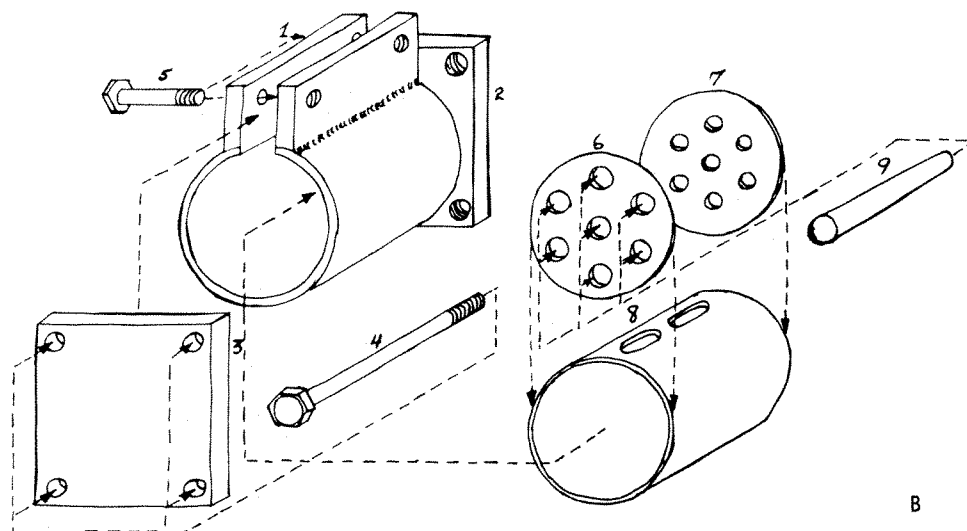


FIG. 4. (B) Mold assembly for honeycomb collimator: 1. mold tube and port; 2. endplate; 3. endplate; 4. endplate bolts (4 needed); 5. mold port bolts (2 needed); 6. large focusing plate; 7. small focusing plate; 8. collimator shell; 9. taper pins (7 needed). Material: brass; pins and bolts: steel.

during the molding process. An outside housing unit is made to hold the end plates and shell together (Fig. 4B). Silicone release agent is used to prevent pins and mold parts from adhering to the lead. In a scattering medium the focus is at 9 cm. Between 5.5 and 10.5 cm. from the collimator face, the sensitivity does not vary by more than 12 per cent (Fig. 5). We have found by testing commercially available units that focusing honeycomb collimators do not necessarily have all these characteristics. It is therefore necessary to test them before use in the scanning system. This is done by scanning a point I^{131} source at varying distances. If the collimator is properly constructed, the data when plotted will give curves similar to those obtained by Miller and Scofield²⁷ (Fig. 3A, b).

(2) One and one-half inch by one inch sodium iodide (thallium) crystal with

(3) Dumont 6292 phototube and

(4) integral pulse height analyzer. Initially the spectrum of I^{131} should be taken at the chosen operating voltage and plotted (see Fig. 6). The operating bias should then be chosen so that all the primary .364 mev. gamma radiation is included. This would

occur at a point in the flat part of the curve 50 to 100 millivolts before the large drop in counts, as illustrated in Figure 6. As the phototube wears out, the spectrum becomes distorted by a widening of the primary peak.

(5) Automatic scanner which was designed specially for brain scans and consists of two vertical mounts holding shielding

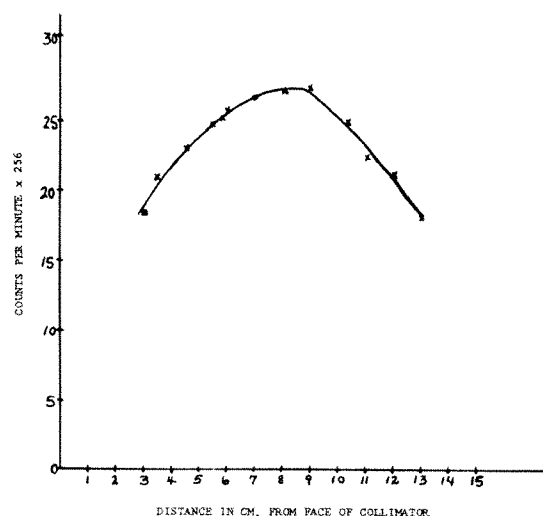


Fig. 5. Response of scintillation counter with focusing honeycomb collimator to I^{131} source in water at different distances from the collimator face.

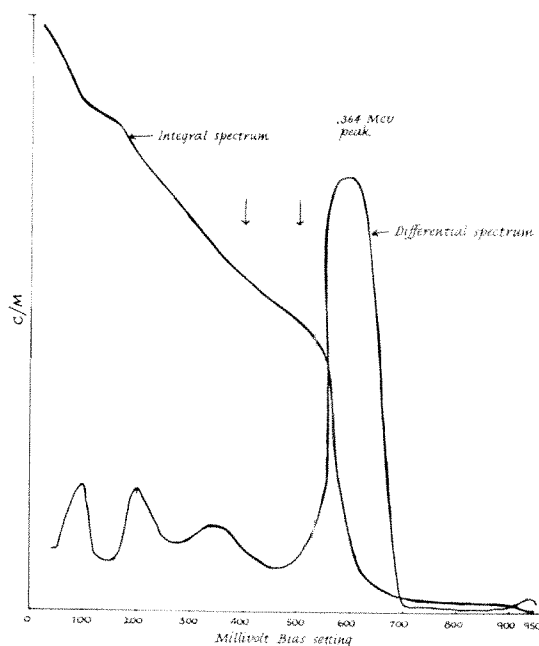


FIG. 6. Spectrum of I^{131} taken with an integral discriminator showing differential and integral plots. Arrows indicate the range for operating bias.

and counters. The patient's head rests between them and both lateral recordings are made simultaneously. Anteroposterior and posteroanterior views may also be obtained. Scans were made with the traverse speed of 7 cm. or 10 cm. per minute. Simultaneous recording by the solenoid print out and the photographic method is carried out. At one time the pen recorder was being used simultaneously with these two systems. Although we have used the pen recorder and the Teledeltos print out system, the interpretation of all of the scans has been from the solenoid print out record or both the solenoid and the photographic (contrast enhancement) method (Fig. 7).

In an attempt to decrease the scanning time, we tried a system of four units, two for each side of the head. However, matching these so that all maintained a similar response was impractical and this approach was abandoned. It is feasible, however, to utilize a multiple counter system if initially the counters are matched using common amplifiers and voltage supplies.

TABLE II
SUBSTANCES USED IN LOCALIZATION STUDIES

Agent	References
Br^{82} , Cl, I	10, 26, 44
P^{32} phosphate	25, 38, 43
Na^{24}	25
K^{42}	25, 37
Cu^{64}	42
As^{74}	positron emitters
Zn^{65}	
Cu^{64} porphyrin	
I^{131} albumin	13, 22, 41
I^{131} tetracycline	39, 40
I^{131} octoiodofluorescein	4
I^{131} antibody to fibrin	9, 15, 36
Hg^{203} neohydrin	17
	31
	3
	9

II. ENHANCEMENT OF UPTAKE

The second major approach to improved statistics of localization lies in the enhancement of uptake in the tumor bed. Over the years various agents have been used in the hope of increasing tumor uptake ratio. These comprise physiologically active substances, including antibodies and compounds specifically related to central nervous system metabolism (Table II).

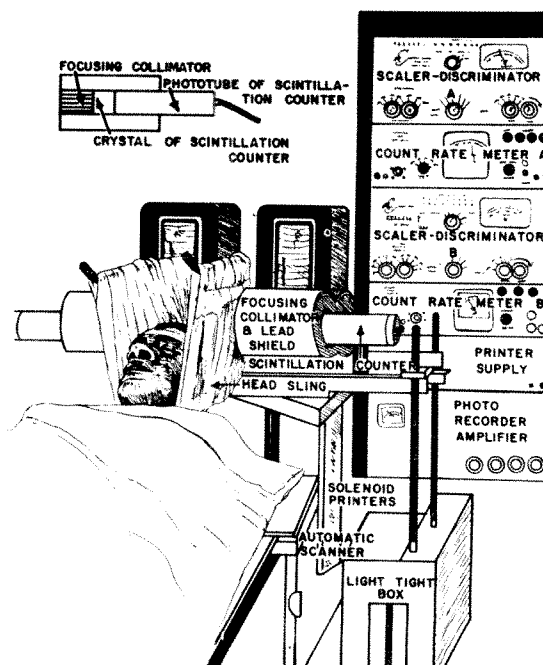


FIG. 7. Drawing of instrumentation and set-up currently in use.

However, iodine tagged human serum albumin continues to be the most useful clinical tool. Because of physical characteristics lending themselves to improved collimation, mercury 203 has been studied in the form of Hg²⁰³ labelled neohydrin.⁹ It has proven inferior to I¹³¹ labelled albumin as an agent in our particular investigations, but further studies are being carried out.

III. RESULTS

In spite of the disappointing efforts in this direction the statistical results are encouraging. A total of 344 cases has been examined. In about 90 per cent of the cases, the dose used was 5 μ c/kg. of body weight. No patient received more than 7 μ c/kg.

Accuracy as referred to below is defined as follows. In normal cases it means that the test agrees with the results of cerebral angiography and/or pneumoencephalography, as well as with the final clinical im-

pression. In abnormal cases the lesion has either been confirmed surgically or by angiography and/or pneumography. A few patients came to autopsy.

The results are summarized in Table III.

In Table IV are listed the lesions not localized and the scanning times.

Several other innovations reported from this laboratory³⁶ have added measurably to the efficiency of the technique. These include repeated scanning and the recognition of a specific time factor for optimal uptake by different types of expanding lesions. Repeated scanning tends to reinforce impressions in questionable localization and eliminate artefacts. Prior to these studies, scanning was presumed to be most effectively carried out after the blood level of isotope had reached a steady plateau. The routine use of scans at the time of injection at 24 and 48 hours makes it possible to completely cover the entire spectrum of optimal uptake times for all the common

TABLE III
STATISTICAL ANALYSIS OF 344 SCANS

No. of Cases	Diagnosis	No. of Cases Accurately Diagnosed	No. of Cases Missed
22	Meningiomas	18	4
63	Gliomas	55	8
37	Mixed Pathology		
	4 Acoustic	4	0
	21 Metastatic	17	4
	2 Glomus	2	0
	1 Neuroblastoma	1	0
	1 Nasopharyngeal	1	0
	2 Carcinomatosis	0	2
	1 Corpus Callosum	1	0
	2 Third Ventricle	1	1
	3 Pituitary	3	0
10	Arteriovenous Malformations	9	1
—		—	—
132		112 or 84.85%	20 or 15.15% False Positives
27	Thromboses and Cerebrovascular Accidents	27	0
136	Normals	134	2
—		—	—
163		161 or 98.8%	2 or 1.2%
49	Unconfirmed, indefinite diagnosis		
344	Total Test Accuracy	273 or 92.6%	22 or 7.4%

TABLE IV
 LESIONS NOT LOCALIZED AND THEIR
 TIMES OF SCANNING
 Analysis of Cases Missed

1 out of 10, 1 Arteriovenous Malformation—small lesion
8 out of 63, Gliomas
3 astrocytomas, scanned at 24, 48 hours
1 astrocytoma, scanned at 24, 48 and 72 hours
1 glioblastoma, scanned at 24, 48 hours
1 glioblastoma, scanned at 24 hours only
1 oligodendroglioma, scanned at 24 hours only
1 small mixed oligodendroglioma—astrocytoma, scanned at 24, and 48 hours
4 out of 22 Meningiomas
2 were scanned only at 24 hours
1 parasagittal, small falx (3 cm.)
1 parasagittal was scanned at both 24, 48 hours
False positives
1 Tuberculous meningitis (confirmed by post-mortem examination)
1 Late syphilis, diagnosis of temporal lobe epilepsy. Pneumoencephalography was normal but arteriography was not done. Electroencephalography showed slow wave focus in same region.

types of space occupying lesions. Sometimes 72 hour scans are taken (Fig. 8).

The general chronologic pattern of up-

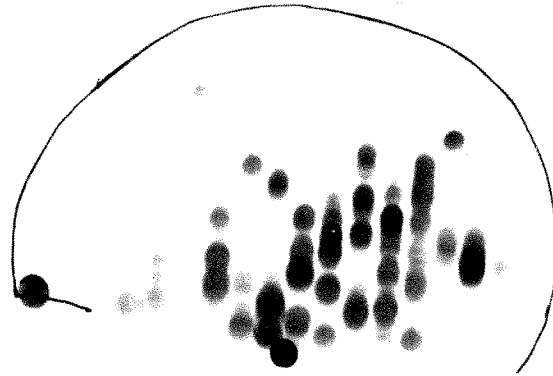


FIG. 9. Left posterior temporo-parieto-occipital angioma (immediate scan).

take is as follows:

(1) Lesions which pre-empt blood supply or which are characterized by unique hypervascularity are best seen immediately after injection. These include arteriovenous anomalies and angioblastic meningiomas. Certain arteriovenous lesions seem to retain the radioactive substance in tumor fashion and remain visible in later scans. This fact may be of significance in separating such lesions into pathologic groups (Fig. 9).

(2) Meningiomas generally appear by 24 hours after injection and tend to be

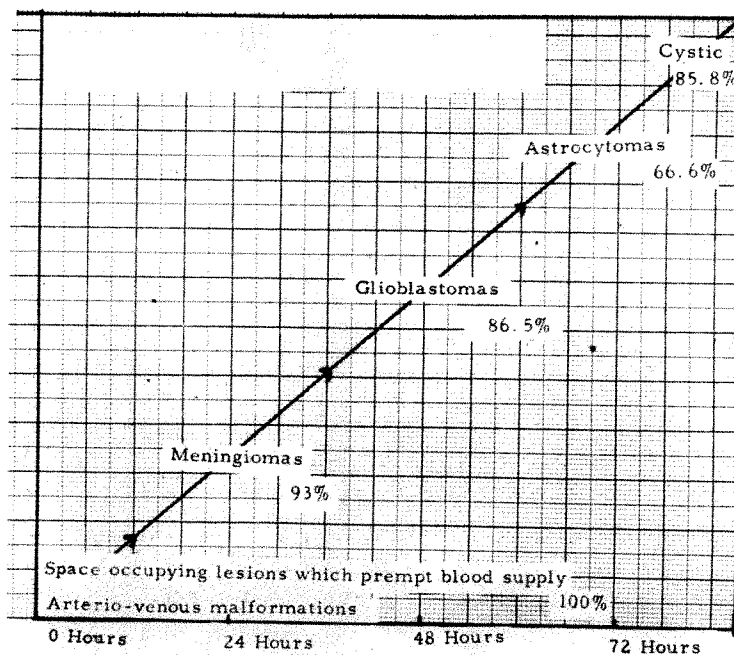


FIG. 8. Effective scan/time relationship. Percentages indicate the lesions seen best at a particular time.

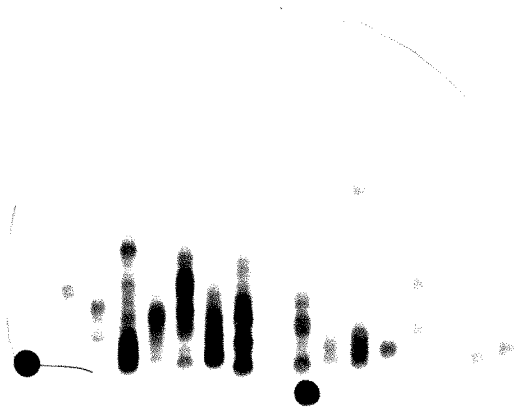


FIG. 10. Olfactory groove meningioma (left 24 hour scan).

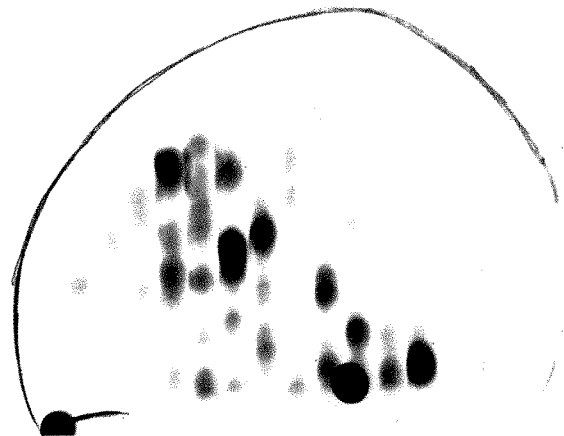


FIG. 12. Left frontal metastasis (24 hour scan).

most vivid within this period (Fig. 10).

(3) Gliomas appear at 24 hours, and become more obvious by 48 hours (Fig. 11, *A* and *B*). The type of scan depends upon the inherent characteristics of the lesion, with avascular astrocytomas poorly seen and glioblastomas seen very clearly. Metastatic lesions follow a similar pattern of appearance. Their multiplicity and small cubic volume in relationship to surrounding edema make them occasionally very difficult to detect (Fig. 12).

(4) Cystic lesions begin to appear late in the scan series and are best delineated after 48 hours (Fig. 13).

In addition to avascular lesions, third ventricular lesions are not well seen. Temporal lobe lesions can be obscured by the heavy concentration of isotope in the overlying muscle. The suboccipital muscle layers create an even greater barrier to easy recognition of cerebellar lesions. In both areas, however, lesions of effective concentrating power are commonly seen (Fig. 14).

It is thus possible not only to increase the statistical accuracy of the method by repeated scanning, but to predict the exact nature of the pathologic lesion by its time of appearance. Such data greatly increase

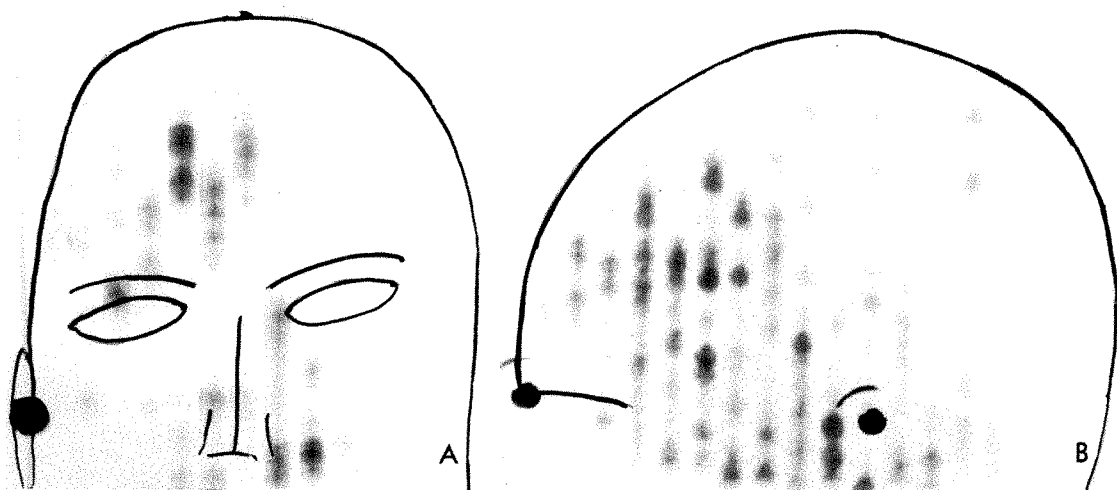


FIG. 11. Recurrent right frontal lobe glioblastoma multiforme (cystic). (*A*) Anteroposterior view and (*B*) lateral view (48 hour scans).

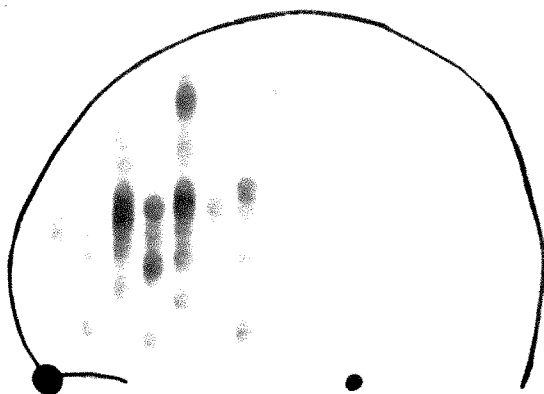


FIG. 13. Postoperative mixed glioma in left frontal parietal region (72 hour scan).

the clinical value of the test.

We have as yet been loathe to suggest operation on the basis of even the most sharply demarcated scans without further definitive studies. In many instances surgical intervention could be carried out without any loss of essential data to the operating surgeon. There are attractive aspects to the method for accurate flap placement. Localization by pneumography depends upon a good deal of complex interpretation which is in turn dependent upon experience and special skills, some intuitive. The appearance of massive shift on an air study may depend upon edema and various mechanical factors, rather than actual tumor mass and the exact locus of chief involvement may be obscured by these sequential factors. Arteriography is a superb test which needs no defense. However, it is almost completely dependent upon either the mechanical displacement of vessels or the presence of an abnormal vasculature within a lesion or in its circumference. In areas where this peculiarity does not apply, localization can be more a deductive discipline than one of frank visualization. It is apparent that isotope scanning has specific advantages and may eventually serve as a preoperative method of localization without recourse to further studies.

In comparing statistical efficiency, certain other facts must be borne in mind. If one considers that even with objective

tests such as arteriography and pneumoencephalography there is a good deal of pre-test selection to eliminate noncontributive studies, the accuracy of the scanning method approaches clinical standards. A carotid arteriogram done on the wrong side, or for a posterior fossa or midline lesion would be a diagnostic failure. Additionally, there is a significant patient risk and also technical failure in both pneumoencephalography and arteriography. These factors certainly militate against using either as a repeated screening procedure or a casual diagnostic test.

Presently, the areas of chief clinical usefulness for isotope scanning are: (1) as a screening test to determine the need for more intensive studies, or for preoperative localization; (2) as a means of prognosticating lesion type (Fig. 15); (3) as a means of analyzing the effects of chemotherapy and radiation therapy without recourse to repeated angiography or air studies (Fig. 16, A-D; and 17, A and B); (4) for follow-up studies of postoperative patients (Fig. 18, A and B); (5) for physiologic studies of the effect of changes in hemodynamics on vascular lesions and the separation of the latter into various categories depending upon their characteristics.

SUMMARY AND CONCLUSIONS

1. Efficient collimation and automatic tracking devices, with improved sensitivity in counting and recording, have made the extracranial localization of space occupying

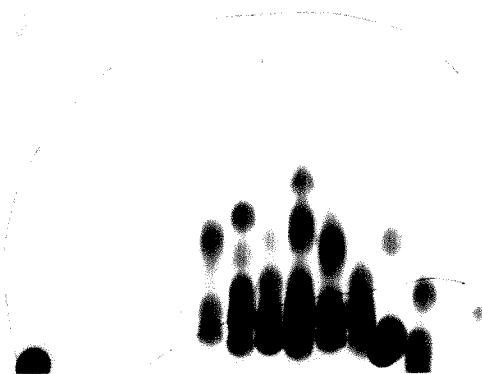


FIG. 14. Right temporal lobe glioblastoma (48 hour scan). Note clarity despite high temporal muscle uptake.

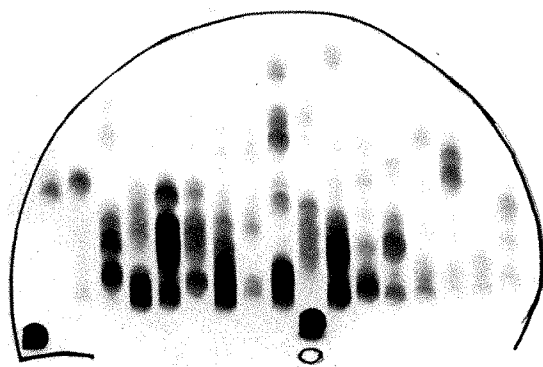


FIG. 15. Left pterion meningioma (immediate scan). The pathologic type is more easily predicted than on the arteriogram.

intracranial lesions with gamma emitters clinically practical despite low differential count rate.

2. Isotope scanning using iodinated human serum albumin meets the need for a reasonably efficient screening test for space occupying lesions of the cerebral hemispheres which can be repeated on multiple occasions without significant radiation hazard.

3. The routine use of repeat scans over a 48 and 72 hour period serves to eliminate false positives and to reinforce the accuracy of interpretation.

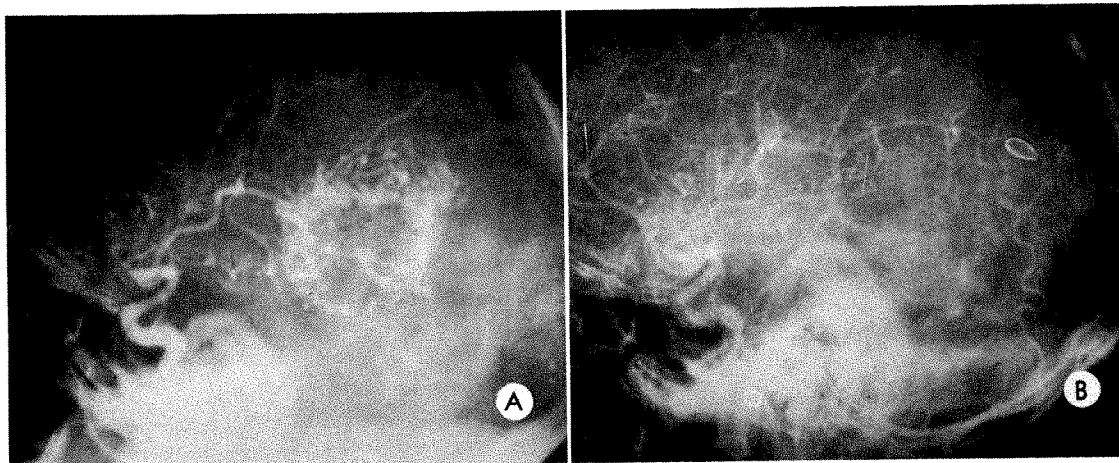


FIG. 16. Right parietal glioblastoma multiforme. Lateral arteriograms. (A) Large vascularized intracerebral tumor. (B) After full course of radiation therapy. Note change.

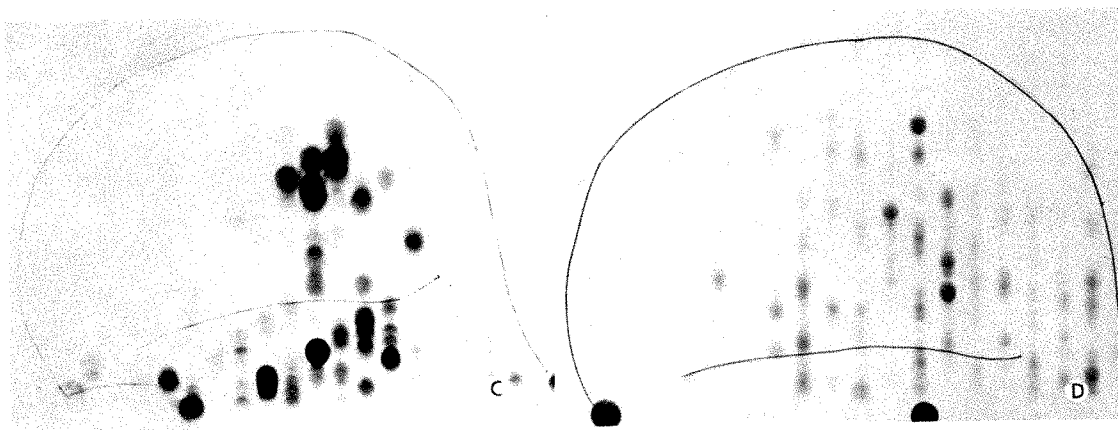


FIG. 16. (C) Scan before radiation therapy shows large vascularized intracerebral tumor (right 48 hour scan). (D) Scan three months after radiation therapy (right 48 hour scan). Note change.

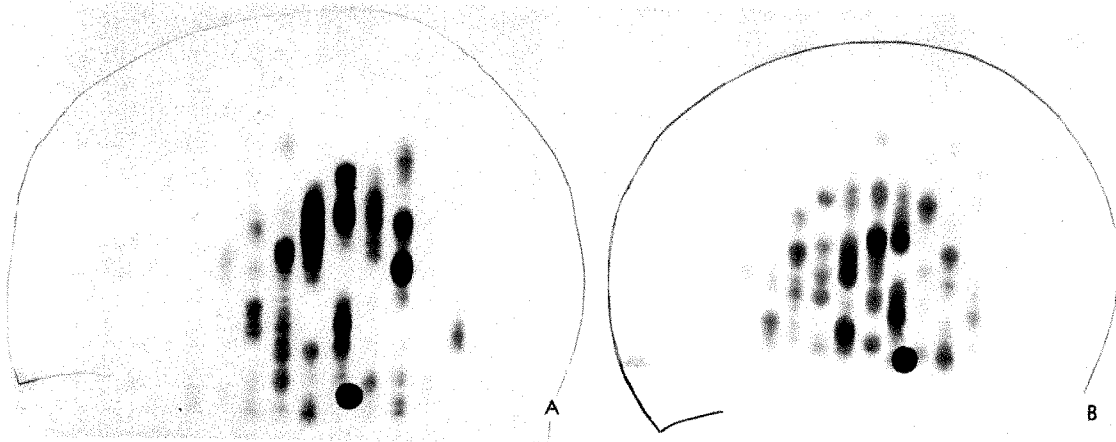


FIG. 17. Right arteriovenous malformation (immediate scans). (A) Before radiation therapy and (B) unchanged after tumoricidal dose of radiation.

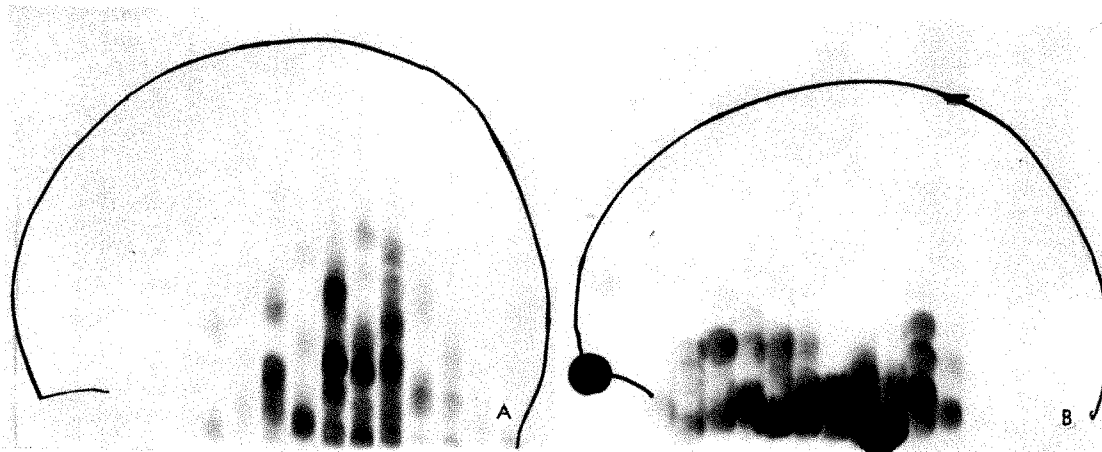


FIG. 18. Glomus jugulare tumor in right petrous bone (immediate scans). (A) After full course of radiation therapy (unchanged) and (B) after ligation of feeding right external carotid artery.

4. The recognition that certain lesions have a maximal differential uptake time has tended to improve statistical success and affords important information about the pathologic nature of lesions studied.

5. Isotope scanning permits intriguing opportunities for gauging the success of experimental therapies without recourse to rigorous testing of the patient.

6. Isotope scanning by the described technique maintains minimal over-all statistical accuracy of 85 per cent for all space occupying hemisphere lesions with negligible false positives.

7. The flexibility of the method, and, in

particular, its accuracy in revealing a wide spectrum of lesion types implies a more general usefulness than other isotope techniques in current usage.

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RADIATION THERAPY IN THE TREATMENT OF INTRACRANIAL TUMORS*

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PRI-MARY tumors arising in the central nervous system are uncommon, constituting only about 2 per cent of all neoplastic disease in the human. Patients with astrocytomas of higher grade (glioblastoma multiforme) cannot look forward to more than a few months of life after surgical excision alone and the outlook for continued life in those with other tumors of this group is little better. The effect of radiation on these tumors is not well known because of their infrequency. In our institution there has been increasing interest in the use of radiation in the treatment of patients with these tumors, and we feel that this can improve the duration and quality of their survival. We wish, therefore, to present our techniques of treatment, to report the results that we have obtained and to compare these results with others that have been reported.

MATERIAL

In the period from January, 1955 through December, 1960, 95 patients were accepted for treatment of a neoplastic growth involving the brain. Of these, 83 completed the planned course of therapy. No meningiomas are included in this group, since it has not been our policy to accept these for treatment due to the relatively good survival of patients after surgery and the reputed insensitivity of this tumor.¹¹ Pituitary tumors and tumors of the spinal cord are also excluded.

Table I shows the distribution of these patients according to the tumor types, using the classification proposed by Kern-

han *et al.*⁹ The various grades of astrocytoma constitute the largest group of patients treated.

In the last two to three years it has been our policy to treat all patients with astrocytoma Grades III and IV (glioblastoma multiforme) who have survived the immediate postoperative period, because their prognosis with surgery alone has been so poor. Ependymoma and medulloblastoma have also been treated by irradiation as a routine procedure, but astrocytoma Grades I and II and oligodendroglioma have been treated only in cases of recurrence. Because of this, the number of low grade astrocytomas does not reflect the frequency of this tumor in general. Other than this, the distribution of tumor types is fairly typical of that reported in other series.

TABLE I
TUMOR HISTOLOGY AND DISTRIBUTION

Histologic Classification	No. Treated	No. Completed Treatment
Astrocytoma	61	54
Grades I and II	7	5
Grades III and IV	45	40
Unclassified	9	9
Ependymoma	3	3
Oligodendroglioma	5	5
Medulloblastoma	7	7
Metastatic Tumors	15	11
Others	4	3
Leptomeningeal Sarcoma	2	1
Hemangioblastoma	1	1
Sarcoepithelioma	1	1
<i>Total</i>	95	83

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METHODS

Tumors arising in the brain have definite growth patterns which determine the treatment plans to be used. While metastasis to regions outside of the cranial cavity is rare, infiltration and extension within the brain are very common. The anatomic division of the brain into two hemispheres tends to restrict transverse extension of tumors arising in the cerebrum though no such restriction exists for anteroposterior extension. Localization of the main tumor mass by means of roentgenography, electroencephalography or surgical exploration is not definite in many instances, and the accurate delineation of the full extent of the tumor infiltration is usually faulty. Concannon, Kramer and Berry⁷ compared tumor extension found at autopsy with arteriographic, pneumoencephalographic and surgical estimates of tumor size and extent. They found that these methods usually underestimated the full extent of the tumor.

On this basis, small field beam-directed therapy would seem to have limited usefulness, and some form of regional therapy would seem indicated. Some years ago, a simple reproducible group of field arrangements was developed by one of us (R.S.Q.) that fulfills these requirements. Some of these field arrangements were described in an article by Richmond¹³ in 1952. Since then the system has been further elaborated. We feel that these treatment plans fulfill the requirements for regional therapy of the brain and warrant further description.

These radiation applications are based on the use of two pairs of coaxially opposed fields arranged at right angles to each other. The central axes of all of these fields lie in one plane which is parallel to the supra-orbital-meatal baseline. This baseline, defined by the supraorbital ridge and the external auditory meatus, quite closely defines the lowest extensions of the cranial fossae in most patients (Fig. 1). The lower edges of the treatment fields are placed along this baseline or its extension.

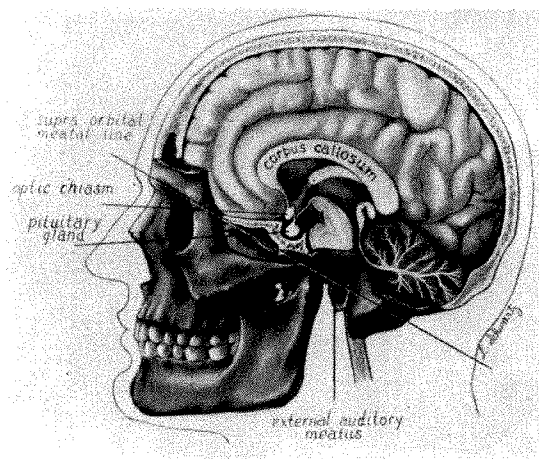


FIG. 1. The location of the supraorbital-meatal base line with reference to the brain and base of the skull.

Using this same basic field arrangement in all instances and shifting the anteroposterior or lateral position of the central axes of the fields, it is possible to vary the position of the high dose region as needed within the cranial cavity and still maintain a regional distribution. Figures 2 through

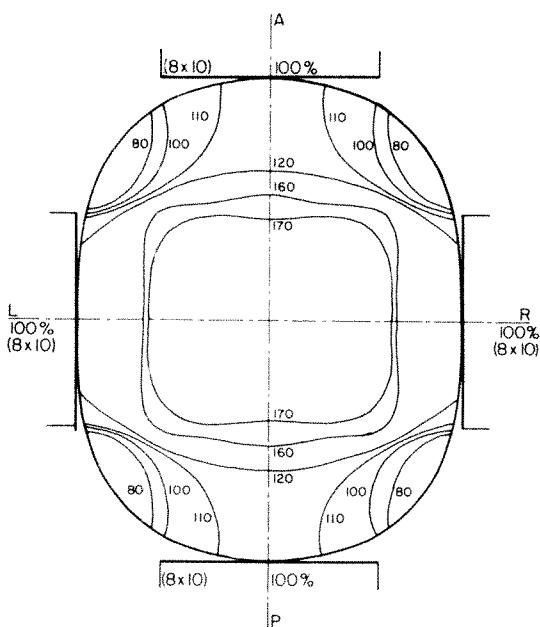


FIG. 2. Basic four field arrangement. The field axes coincide with the anteroposterior and lateral midlines of the skull. All fields equal in size with equal doses given through each. Note the centrally located symmetrical high dose region.

to show the possibilities of these arrangements. A great majority of the patients reported in this study have been treated with field arrangements following these principles. We have found them to be easy to apply and reproduce, and to be well tolerated.

The maximum dosage given to these patients has been limited to 4,000 r in 30-35 days. This quantity was chosen as a safe dose that would minimize the probability of late radiation necrosis of the brain on the basis of the studies of Arnold, Bailey, Harvey, Haas and Laughlin¹ and Boden.^{4,5} The doses were calculated without allowance for absorption by the bones of the cranial vault, and thus the actual doses in the brain may be as much as 10 per cent less than those calculated. Radiation generated at 250 kv. (added filter .44 mm. Sn, .25 mm. Cu, and 1.0 mm. Al) with a half-value layer of 3 mm. of Cu has been used in almost all instances since the desired tumor dose could easily be achieved without exceeding the tolerance of the skin or other tissues. Temporary epilation and

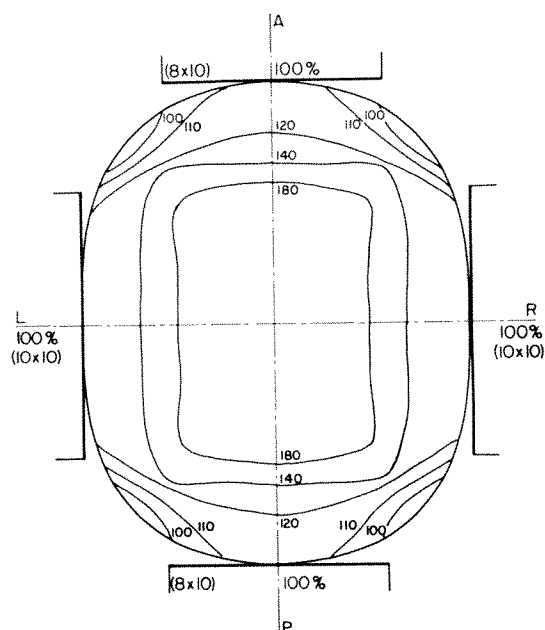


FIG. 3. Extension of the maximum dose region anteroposteriorly by widening the lateral fields but retaining equal dosage.

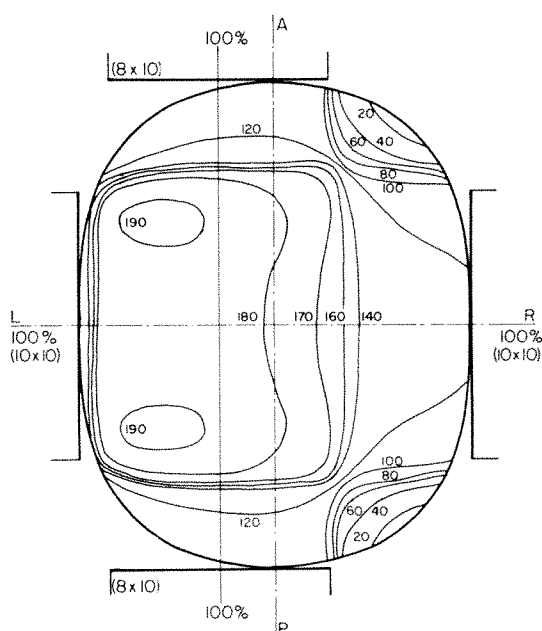


FIG. 4. The anteroposterior field pair has been shifted laterally by 2 cm., with shift of the zone of maximum dose. With equal dosage applied to all fields, there is excessive dose to the peripheral tissues.

the production of a moderate erythema in the treatment field are usual. Permanent epilation has not occurred. It has been our

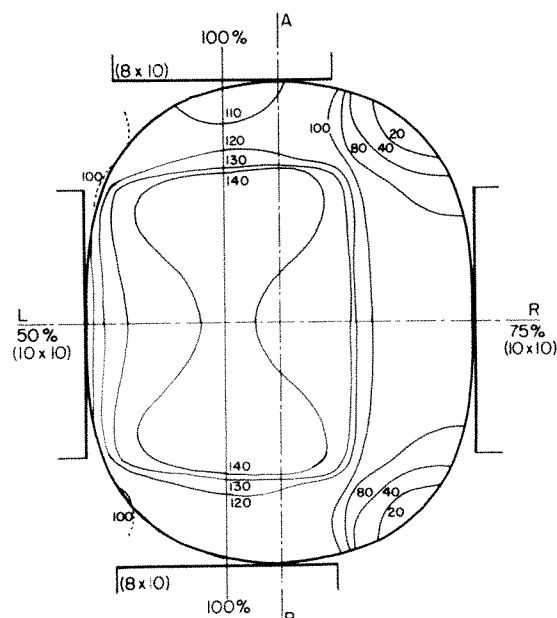


FIG. 5. A reduction in the dose given to the lateral fields improves the situation.

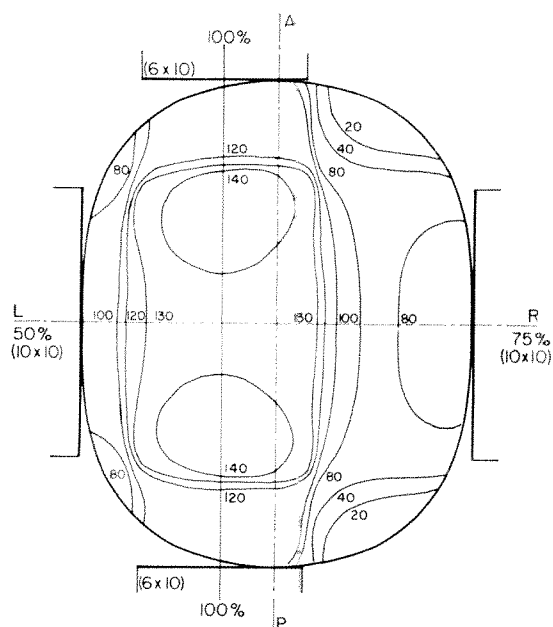


FIG. 6. Further improvement is achieved by narrowing the anterior and posterior fields.

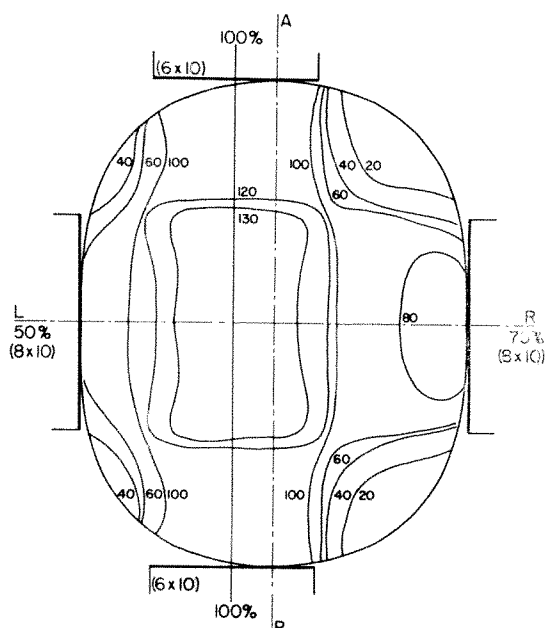


FIG. 7. The anteroposterior extent can be reduced by reducing the width of the lateral fields. The last two figures represent clinically satisfactory arrangements that have been found quite useful.

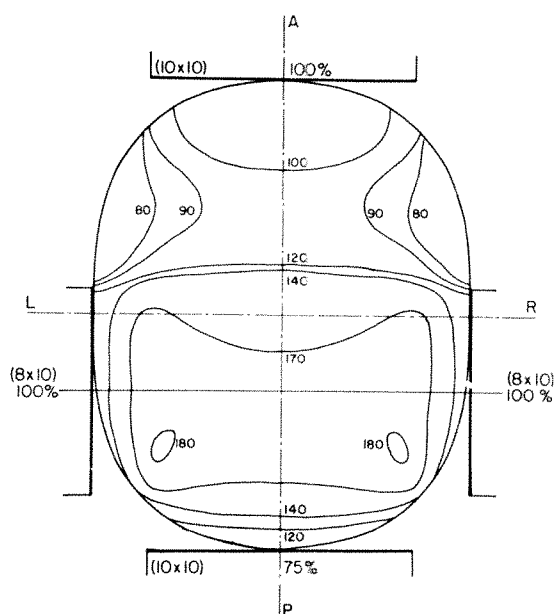


FIG. 8. Shifting the lateral pair of fields posteriorly will shift the zone of maximum dose posteriorly. The same would apply to an anterior displacement.

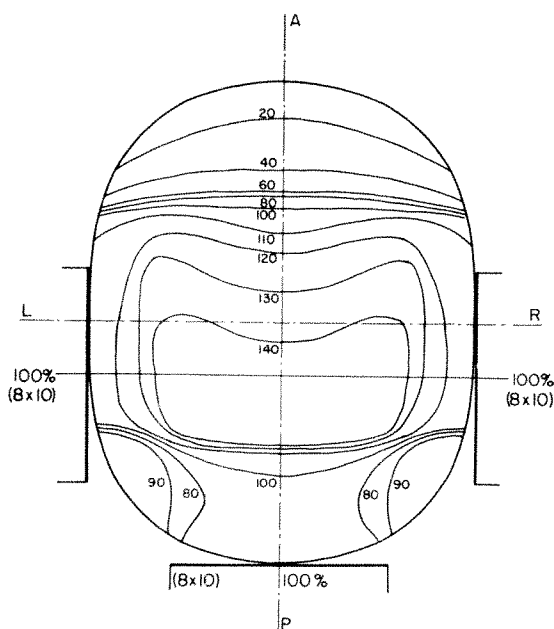


FIG. 9. For an anterior or posterior fossa lesion, one of the anteroposterior pair of fields may be dropped.

policy to treat every field each day, and it is possible that any other cycling of the treatment fields might increase the skin reaction.

Because of the hazard of brain edema during the early phases of treatment, the initial doses are considerably reduced, the full daily tumor dose increment of 200 r not being achieved before the sixth or seventh day of treatment.

RESULTS

Since we are dealing with a diverse group of tumors, no over-all survival figure is given. Most groups are quite small and the follow-up is relatively short, thus the results are reported in terms of actual survival in months from the closing time of the series. Astrocytomas Grades III and IV constitute the largest single group and will be discussed in greater detail separately.

In Table II are seen the results of the treatment of low grade astrocytomas. The patients were largely treated for recurrence, hence the poor survival rate. Table III presents the survival results in patients with tumors involving the brain stem and midbrain. A few of the tumors in this group were biopsied. Most of them were not because of the location. The good survival rate in this group is quite typical of that reported by others. Oligodendroglioma and ependymoma are relatively rare tumors and are few in number. The results are presented in Table IV. As can be seen,

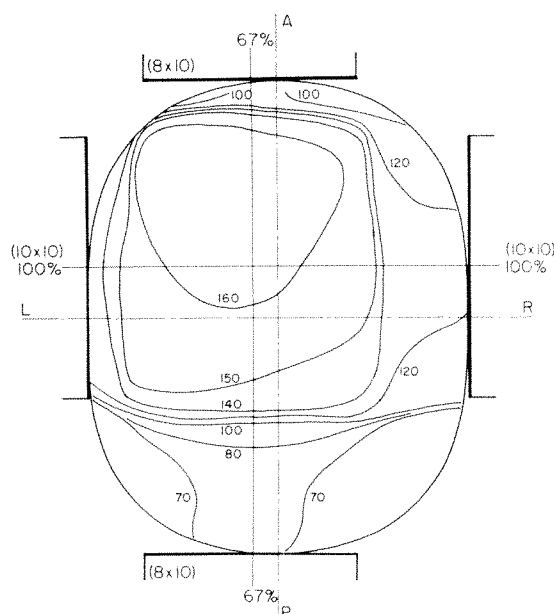


FIG. 10. Shift of both pairs of fields and adjustment of individual dosage permit the development of a high dose region limited to one quadrant.

the survival rate in this group also is quite good.

The group of medulloblastomas which we have seen is somewhat unusual in the proportion of older patients treated (Table v). It is interesting to note that nearly all of the long-term survivals have been in patients under eleven years. The two patients still living both fall in this age group.

TABLE II
ASTROCYTOMA GRADES I AND II
LENGTH OF SURVIVAL

No. of Patients	Alive (mo.)	Dead (mo.)
2	4	
1	61	
1		1
1		5
1		6
1		18
Total 7	3	4

TABLE III
ASTROCYTOMA, GRADE UNDETERMINED
LENGTH OF SURVIVAL

No. of Patients	Site	Alive (mo.)	Dead (mo.)
1	temporal lobe		32
2	corpus callosum		3
1	midbrain	12	
1	midbrain	31	
1	brain stem	39	
1	pons	37	
1	septum pellucidum	35	
Total 8*		5	2

* One patient lost to follow-up.

TABLE IV
OLIGODENDROGLIOMA AND EPENDYMOMA
LENGTH OF SURVIVAL

OLIGODENDROGLIOMA		
No. of Patients	Alive (mo.)	Dead (mo.)
1	8	
1	12	
1	24	
1	31	
1		32
Total 5	4	1
EPENDYMOMA		
No. of Patients	Alive (mo.)	Dead (mo.)
1	61	
1	66	
1		9
Total 3	2	1

This age distribution may account for the relatively poor showing of this group of tumors, as compared with those of Bouchard and Peirce,⁶ and Paterson and Farr.¹²

Somatic tumors metastatic to the central nervous system form a group in which the value of specific therapy is difficult to evaluate. Total patient survival is pri-

marily dependent on the behavior of the neoplasm in other sites, and thus survival data are not helpful in evaluation. In our group there are a few patients in whom the relief of symptoms due to the cerebral metastases has been spectacular, and in general most patients have benefited symptomatically, but few have lived long enough to make the expenditure of time and money clearly worthwhile. In selected patients in good physical condition with little evidence of other metastases, cranial irradiation is worthwhile. Such favorable cases are most often found among patients with carcinoma of the breast. The overall life expectancy in carcinoma of the lung is so short that treatment of intracranial metastases is rarely of value.

Mere evaluation of survival figures does not give the true picture of the benefit of a treatment. In Figure 11 we have attempted to indicate the functional status of the entire group of patients 6 to 8 weeks after treatment, *i.e.*, after subsidence of treatment reaction. Figure 12 shows the relative functional status of patients with astrocytoma Grades III and IV after surgery alone, and after surgery and irradiation. In order to make the groups more comparable, only patients surviving surgery by at least one month are included.

TABLE V
MEDULLOBLASTOMA
LENGTH OF SURVIVAL

No. of Patients	Age when Treated (yr.)	Alive (mo.)	Dead (mo.)
1	2	72	
1	7	42	
1	11		41
1	12		2
1	12		5
1	13		44
Total 6*		2	4

* One patient lost to follow-up.

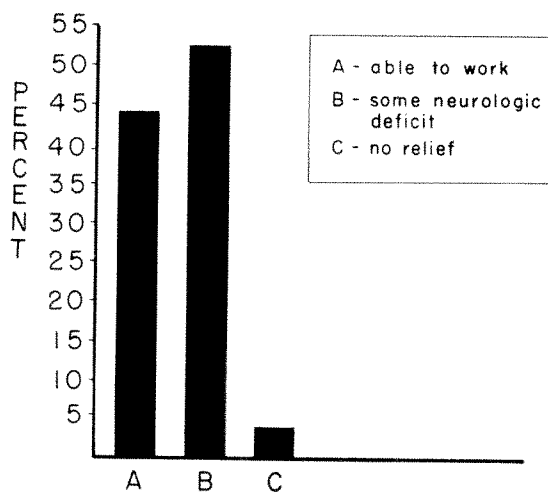


FIG. 11. Status of all radiation therapy patients 6 to 8 weeks following therapy.

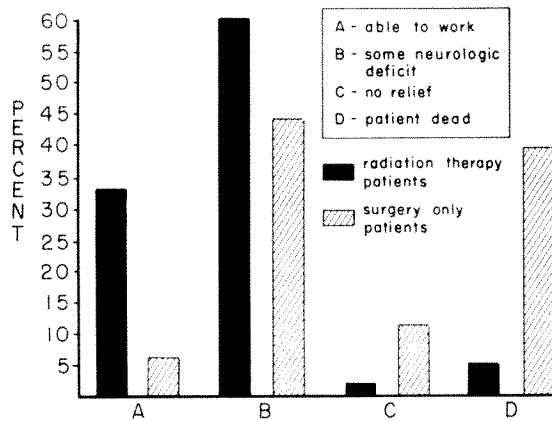


FIG. 12. Status of radiation therapy and surgery patients with astrocytoma Grades III and IV, 6 to 8 weeks after therapy.

DISCUSSION

Evaluation of the benefits of irradiation is particularly difficult when treatment is given after partial surgical extirpation of tumors. A comparison of the patient survival rate after surgery alone and after combined surgery and irradiation is crucial, if the two groups are otherwise comparable. Since a high proportion of the patients in this hospital with astrocytoma Grades III and IV receive postoperative irradiation, we could only find a small group who had been treated by surgical removal alone. The size and distribution of the two groups are shown in Figure 13.

The number of patients involved in our

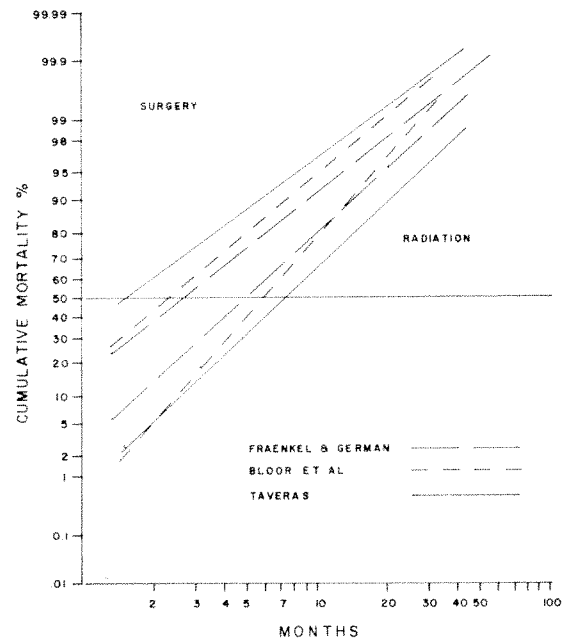


FIG. 14. Relative mortality of patients with astrocytoma Grades III and IV after surgery alone, and surgery plus postoperative irradiation. (Frankel and German⁸ and Taveras¹⁴)

two groups is very small. A review of the literature disclosed two recent studies of this same problem. Frankel and German⁸ and Taveras¹⁴ present comparisons of patients treated with surgical extirpation and irradiation, and with surgery alone. In Figure 14 the cumulative mortality at various intervals after treatment is plotted for these two series as well as our own. To

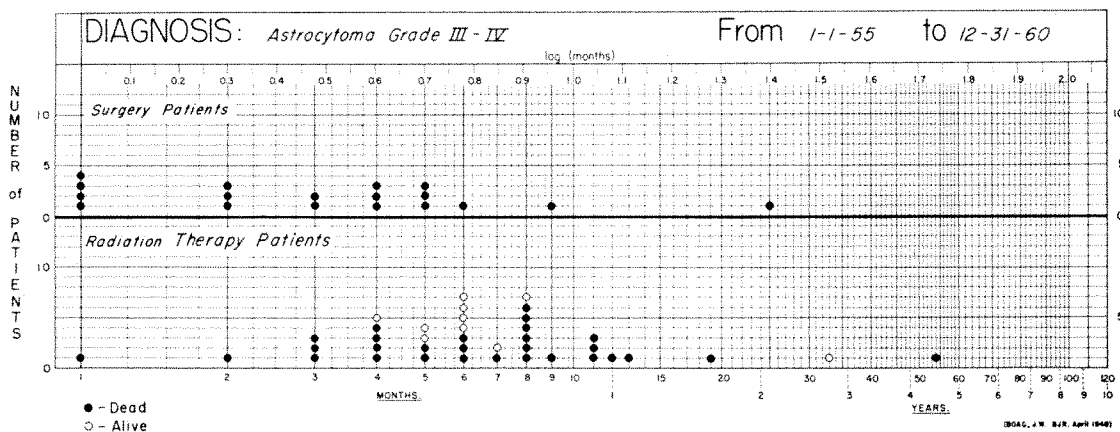


FIG. 13. Survival status of patients on December 31, 1960.

obtain the individual points from which the curves were plotted, the data given in their reports as line graphs of per cent survival were converted into numbers of patients surviving at each interval and then into cumulative mortality. The plots were then made on a logarithmic probability scale as suggested by Boag.³

There is a definite division of the surgical mortality curves and those of patients after irradiation into separate groups in Figure 14. Because of this division, we felt justified in combining all of the surgical groups as well as the radiation groups into single curves (Fig. 15), again returning to the calculated numbers of patients at each interval. The larger numbers in the combined groups eliminated some of the irregularities found in making the other plots, and an excellent fit was obtained with the straight line curves shown. These curves show a distinct difference in both position and slope. The median survival for patients treated with surgical extirpation alone is two months, while that for surgical intervention followed by irradiation is six and one half months.

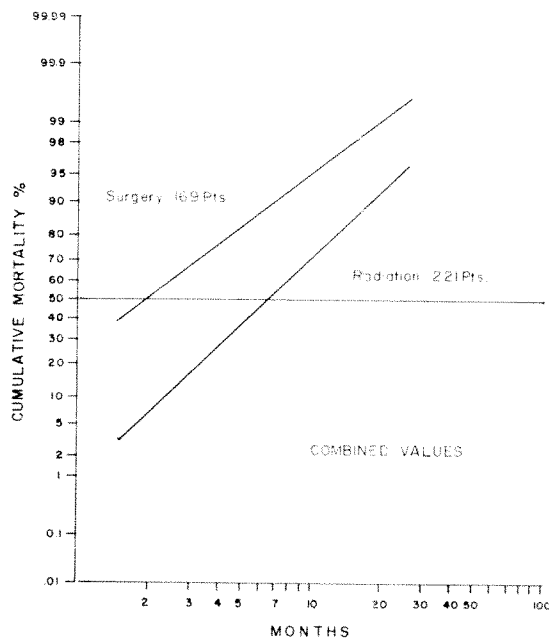


FIG. 15. Astrocytoma Grades III and IV. Comparison of cumulative mortality curves for a combination of the groups shown in Figure 14.

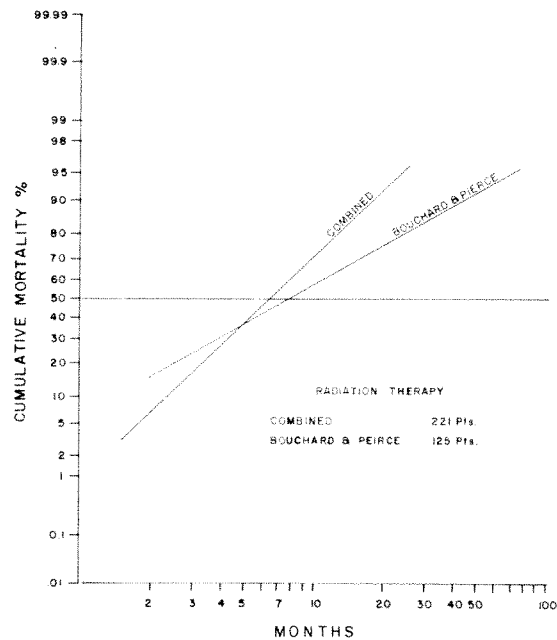


FIG. 16. Astrocytoma Grades III and IV. Comparison of combined data of patients receiving radiation therapy from Figure 15 and data from Bouchard and Peirce.⁶

tion is six and one half months.

The report by Bouchard and Peirce⁶ in 1960 comprises the largest collection of patients treated with surgery and post-operative radiation that has yet been presented. The follow-up period is also exceptionally long. When their results with astrocytoma Grades III and IV are presented in comparison with the combined results mentioned above, there is noted to be a distinct difference in slope of the two curves though the median survival is not greatly different (Fig. 16). Unfortunately, their paper gives no information regarding patients surviving less than one year, nor on their criteria for selection of patients for radiation therapy. Bouchard and Peirce⁶ report the use of radiation doses of 5,000–6,000 r in about 50 days which is larger than that used by Taveras (4,000–5,000 r in 4–5 weeks), Frankel and German (at least 4,000 r) or by us (maximum of 4,000–4,200 r in about 30 days). It is quite possible that the greater protraction to a higher total dose may be responsible for the dif-

ference in survival rate of their patients, but the other factors mentioned could also produce this difference.

Our experience with postoperative irradiation in the treatment of intracranial tumors other than astrocytoma of Grades III and IV is insufficient to permit conclusions as to its value. The results which we have obtained are in general accord with those reported by other authors with the exception of medulloblastoma. Here, the peculiar age distribution in our group of patients may account for the difference.

The improvement in survival of patients with high grade astrocytomas treated with postoperative irradiation seems quite definite on the basis of our results and on the results of others. The value of this survival to patients and their families cannot be evaluated objectively. Our experience suggests that the management of these patients during their survival period is facilitated, and that a significant proportion can return to work after irradiation. On these grounds, we feel that this is a procedure that should be more generally used.

What of the future? Can therapeutic irradiation make a greater contribution to the management of these patients than it does now? The amount of our doses has been limited by our concept of brain tolerance obtained from Boden.⁴ To date we have not observed any overt evidence of brain damage from these treatments, so we feel that these are safe doses. Bouchard also disclaims evidence of brain necrosis resulting from the somewhat different dose-time relationship that he has employed. The most recent and most exhaustive study of brain tolerance in irradiated humans is that of Lindgren.¹⁰ The dose-time relationships used by both Bouchard and ourselves lie slightly below his estimate of the threshold for the development of brain necrosis and well below that dose which carries a great risk of cerebral necrosis. From his data it would appear that we could increase our dose to about 5,000 r in the same over-all time with only mod-

erate risk. On the other hand, Bouchard's data suggest that an improvement in results might be obtained by greater protraction with the same equivalent dose. It is our intention to explore both of these possibilities.

SUMMARY

1. In the past six years we have employed radiation in 95 patients with intracranial neoplasms, and have completed therapy to a dose of 4,000-4,200 r in four to five weeks in 83 of these.

2. We have used a standardized, reproducible treatment plan which is described.

3. Our results suggest that radiation therapy is of value in the management of a variety of intracranial tumors.

4. Postoperative irradiation improves both the quality and duration of the survival of patients with astrocytoma Grades III and IV (glioblastoma multiforme).

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SHOULD WE TREAT GLIOBLASTOMA MULTIFORME? A STUDY OF SURVIVAL IN 425 CASES*

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IT IS well known that glioblastoma multiforme is close to being the most malignant neoplasm which occurs in humans. Its growth rate is extremely rapid, and in a few months it may grow so much as to render a previously healthy individual utterly useless. This is particularly true in view of the usual location of this neoplasm, the cerebral hemispheres.

The natural history of glioblastoma indicates the duration of the disease to be seven to fourteen months *from the first symptoms until death*. Very few patients survive beyond this fourteen month period without treatment. The question is whether it is possible to modify this relentless course significantly with the forms of treatment at our disposal at the moment.

The answer to the moral question as to whether treatment of a given disease should be applied is a matter for individual consideration, and in this we are not referring to nursing care, but rather to specific treatment. Obviously, if we have no specific treatment for a disease, none can be applied. Could partial surgical removal and/or radiotherapy be considered as specific treatment? At the present time nothing better can be offered patients with glioblastoma multiforme. While these are far from being specific forms of therapy, they are capable of modifying the course of the disease. It is the purpose of this presentation to try to elucidate whether such treatment has been worthwhile in the management of these tumors, based on a study of 425 histologically verified cases.

PATHOLOGY

As to glioblastomas that occur in the cerebral hemispheres, there is no particular site of predilection, for they may occur in the frontal, temporal, parietal and occipital areas as well as in the thalamus and the corpus callosum. They do not usually occur intraventricularly except by invasion from without. Glioblastomas may also involve the brainstem and, rarely, the spinal cord. They do not occur in the cerebellum. Seeding to other portions of the central nervous system by way of the cerebrospinal fluid and continuous growth superficially along the leptomeninges are not uncommon. Distant metastases are extremely rare. This does not mean that glioblastoma cells are unable to grow outside of the central nervous system. Indeed they are able to do so, and very rapidly. This is exemplified by a case of an obstructive lesion due to glioblastoma which required a shunting procedure. A ventriculopleural shunt was carried out; the shunting tube was an easy path for the free glioblastoma cells which grew rapidly in the chest cavity involving the pleura extensively, the mediastinal lymph nodes, and the bone marrow of the ribs, sternum and vertebral bodies.⁵

Our pathologic laboratory classifies these tumors into (1) glioblastomas and (2) astrocytomas with glioblastomatous changes. This is equivalent to the astrocytomas Grade IV and III respectively according to Kernohan's classification. Of the total number we are reporting, only 10 per cent were classified by our pathologists as

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astrocytomas with glioblastomatous changes (Grade III). This type grows somewhat more slowly than the frank glioblastomas. Some tumors were diagnosed as being an astrocytoma on a first biopsy, whereas a subsequent biopsy performed for recurrence revealed a glioblastoma. It is possible that in these cases tissue representative of the entire tumor was not obtained on the first biopsy; *i.e.*, a segment of a glial tumor may have been classified by the pathologist as astrocytoma, although an area next to it could yield pure glioblastoma. It is also possible that an astrocytoma may become more malignant with the passage of time, a process which occurs in neoplasms arising in other parts of the body.⁴

MATERIAL

Our material consists of 425 cases of glioblastoma, verified by biopsy, seen at the Neurological Institute during a thirteen year period from 1943 through 1955. These were observed during a period when 4,839 tumors of the central nervous system of all types were seen at the same institution. Forty-two cases (10 per cent) were diagnosed as astrocytomas with glioblastomatous changes (Grade III). Six cases were diagnosed as astrocytoma on the first biopsy, and as glioblastoma on the second biopsy taken after recurrence of symptoms (Table I). There were 257 male (60 per cent), and 168 female (40 per cent) patients. The age distribution is given in Table II, 365 of the 425 cases (86 per cent) occurred between the ages of forty-one and seventy.

Location. Two hundred and ten cases (almost exactly 50 per cent) presented in the dominant hemisphere, 195 in the non-

TABLE I
HISTOLOGIC DIAGNOSIS

Glioblastoma.....	377
Astrocytomas with glioblastomatous changes..	42
Astrocytoma on first biopsy, glioblastoma on second biopsy.....	6
Total.....	425

TABLE II
AGE DISTRIBUTION

Decade (yr.)	No. of Patients
1-10.....	2
11-20.....	6
21-30.....	9
31-40.....	38
41-50.....	100
51-60.....	175
61-70.....	90
71-80.....	5
Total.....	425

dominant hemisphere, and 20 could not be classified as to precise location because they involved primarily the corpus callosum. The location as to the lobes of the brain is summarized in Table III. In 180 patients, the glioblastoma was found in the anterior (42.5 per cent), and in 230 in the posterior half of the brain including the temporal lobe. The corpus callosum and deep tumors could not be localized as to lobes.

It is apparent from these figures that glioblastomas have no predilection for any specific area of the brain, but rather their location is related to the relative size of the lobes.

TREATMENT APPROACH

Prior to 1948 the prevailing philosophy

TABLE III
SITE OF GLIOBLASTOMAS

Frontal lobe.....	133
Frontoparietal.....	47
Parietal.....	41
Temporoparietal.....	30
Parieto-occipital.....	23
Temporal.....	136
Corpus callosum.....	12
"Deep".....	3
Total.....	425

Of the temporal tumors 17 were classified as anterior, and 11 as posterior temporal in location.

at the Neurological Institute was that treatment of glioblastoma was not considered worthwhile. Of 114 patients seen in the period between 1943 and 1947, inclusive, 41 (36 per cent) had a partial resection, but only 19 of this total group received radiation therapy. After 1948 an attempt was more often made to provide a radical surgical decompression by tumor removal when necessary by as much resection of the lesion as possible when the tumor was in a favorable location. Of 311 cases seen between 1948 and 1955, partial resection was accomplished in 136 (44 per cent). Frontal and anterior temporal tumors, particularly those in the nondominant hemisphere, lent themselves more readily to a partial or subtotal resection. On the other hand, parietal and parieto-temporal glioblastomas tended to extend so deeply that usually only a small portion of the neoplasm could be removed. Following recovery from the surgical intervention, radiation therapy was given unless the patient was so ill that it was thought he would probably die within the ensuing days. However, some surgeons did not refer any of their patients for radiation therapy following surgical intervention.

In the years before 1953 the dose of radiation which was used was generally lower than that given in the last three years of the study. The first course of treatment usually consisted of a tumor dose of 1,800 r to 2,000 r, given in 2 to 3.5 weeks. A second course of treatment of approximately 1,500 r tumor dose given in about 3 weeks was frequently delivered within the ensuing 3 months. In the last three years (1953 through 1955) a single protracted course of 4,000 r tumor dose in 4-5 weeks was usually delivered, with two exceptions: (1) in the frontal and frontoparietal region 5,000-5,500 r in 6 weeks was used; (2) tumors with radiologic and clinical evidence of deep extension received only 2,500 r tumor dose in 3 weeks, particularly those in the dominant hemisphere. The field size was always ample to cover the tumor bearing area. In a small number

of cases whole brain irradiation was carried out for a midline dose of 2,500 r in 4 weeks.

RESULTS OF TREATMENT

Because the duration of symptoms prior to histologic diagnosis varies with the location of the tumor and with the ability of the patient to observe his own illness, it was thought wise to use the *date of diagnosis* to compute survival times in all of these cases.

It is understood that some patients with glioblastoma are only partially disabled, until the final few weeks before death, whereas others are severely or totally disabled for a long time or throughout their illness. In a study of brain tumors one should therefore consider survival and function. In the group reported by Frankel and German² only 40 per cent had slight or no disability; 33 per cent were severely disabled. Yet, the only absolute criterion to evaluate the results of treatment is the duration of life, since surgical and radiation treatment very often result in temporary improvement of the patient's disability, without prolonging the patient's life. Unfortunately, observations related to the patient's neurologic conditions during the disease, some of which are subjective and some objective, cannot be used effectively in a statistical evaluation because of the many variable factors. For these reasons only survival time statistics will be presented.

It was first decided to establish the average survival curve for our own cases (Fig. 1), using the years 1943 through 1947 when most patients had a simple biopsy and no radiotherapy (64 out of 114). The curve shows that 95 per cent of the patients were dead three months after simple biopsy; all were dead within six months.

This curve may be compared with that obtained from all cases undergoing partial surgical removal only (Fig. 2). As expressed on the operative note the amount of tissue removed varied from "partial removal" to "subtotal removal." As can be seen 86 per cent of patients were dead six months after surgical intervention, 96 per cent were dead twelve months after surgery.

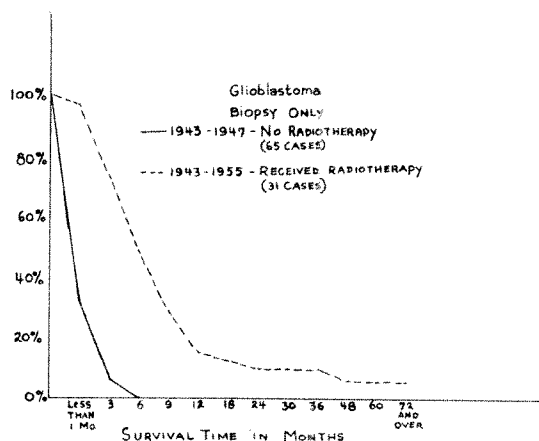


Fig. 1. The solid black line represents the patients who had biopsy only during the 1943-1947 period when most patients were so handled to establish a baseline for survival. The dotted line represents the total number of patients from 1943 through 1955 who had a simple biopsy followed by radiation therapy.

The dotted line curve on Figure 1 represents the patients who had simple biopsy followed by a variable amount of radiation therapy. Fifty per cent were alive six months after biopsy. Two lived over four years. In this study any patient who received more than a few treatments was considered in the group that received radiotherapy. The dotted line curve on Figure 2 represents the group having partial resection followed by radiotherapy. Sixty-eight per cent were alive six months

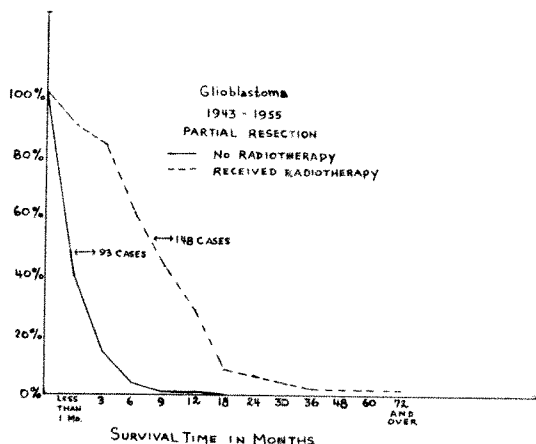


Fig. 2. The curves include all patients who had partial resection in the thirteen year period.

while 32 per cent were alive twelve months after diagnosis.

A full course of radiotherapy requires that a patient live at least one month. Some patients died during the first month while receiving radiation therapy, but these were far fewer than those not subjected to radiotherapy. In this group only 7 per cent died while receiving radiotherapy in the first month, whereas 38 per cent of those not treated by radiation died within the first month: the former were on the average not as ill as the second group.

For these reasons it was thought worthwhile to tabulate the two groups of cases using only patients who had lived at least thirty days (Fig. 3). Another graph of patients living at least sixty days following partial resection showed no difference in the survival curve.

Survival curves were also plotted in relation to the dose of radiation used. They were divided into 4 groups: (a) those receiving under 2,000 r, usually around 1,800 r, which included almost all cases treated prior to 1948 and almost half of those treated up to 1953; (b) those receiving 2,000 to 2,900 r, *i.e.*, almost half of those

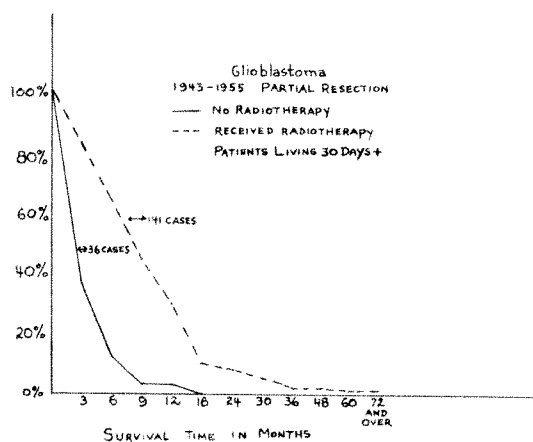


Fig. 3. The curves are based on patients living thirty days or longer in order to eliminate the large group of patients who died in the initial thirty days following either biopsy or partial resection. Essentially no difference in the survival curve was noted when it was compared with another set of curves based on a minimum survival of sixty days.

treated between 1948 and 1952 and about a third of those treated in the 1953-1955 period, as explained under "Treatment Approach"; (c) those receiving 3,000 r to 3,900 r; and (d) those receiving 4,000 r to 5,500 r (Fig. 4).

It can be seen that while those receiving 2,000 r or less had a shorter average survival (50 per cent were dead in six months), there is no significant difference between those receiving 4,000 to 5,500 r and those receiving from 3,000 to 3,900 r. It is interesting to note from the curves in Figure 4 that *regardless of radiation dosage about 90 per cent of the patients were dead at eighteen months*.

Another comparison was made between the group having only biopsy followed by radiotherapy and the one having partial resection plus radiotherapy (Fig. 5). Patients

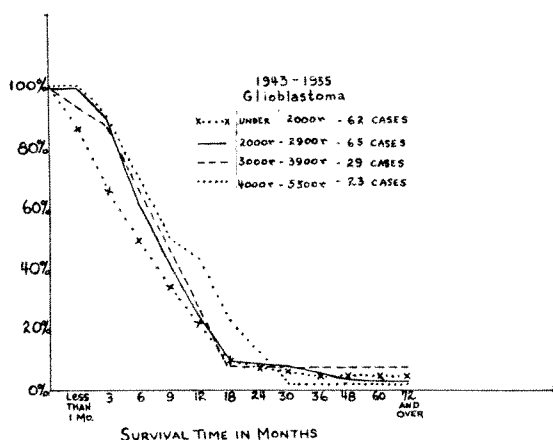


FIG. 4. The curves include all of the patients who received radiotherapy in a thirteen year period to compare survival in relation to dose. From these curves it would appear that there is no significant difference between patients receiving over 2,000 r; however, there appears to be a significant difference when the patients receiving over 2,000 r are compared with those receiving under 2,000 r, indicating that a dose of at least 2,000 r should be delivered. At twelve months there appears to be a slightly better percentage survival rate in the group receiving 4,000 r and up, but at twenty-four months and later there is no significant difference and, in fact, the percentage of patients receiving 4,000 to 5,500 r who survived five years or longer is lower than in the other groups, as explained in the text.

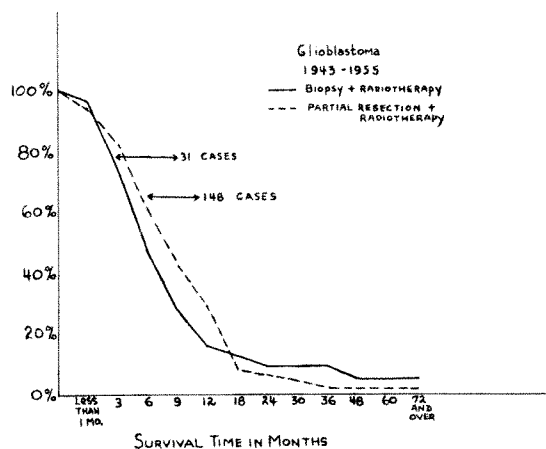


FIG. 5. A comparison is made of the survival time of patients who had biopsy plus radiotherapy and those who had partial resection followed by radiotherapy. There is only a slight improvement in the results when partial resection plus radiotherapy is used. However, at nine months there is approximately a 43 per cent survival in patients with partial resection plus radiotherapy, whereas biopsy only yields a 28 per cent survival.

with partial resection plus radiotherapy had a better survival curve (43 per cent lived nine months) than those who had only biopsy followed by radiotherapy (28 per cent lived nine months) in the period up to eighteen months. In addition, partial removal provides a decompression which has often resulted in rapid improvement of the patient's neurologic status.

The material was analyzed to see whether various factors such as sex, age of patient, and location of the tumor had any influence on survival. No significant differences were encountered. No difference was noted between females under and over forty years of age. Patients with tumors in the dominant hemisphere did not die sooner than others. The same applied to frontal tumors when compared to those situated posteriorly. In fact, all tumors in all locations and in patients of all ages, regardless of whether they were pure glioblastomas or astrocytomas with glioblastomatous changes, showed this inexorable course, modified by radiation therapy, to the point where approximately 10 per cent were alive eighteen months after diagnosis.

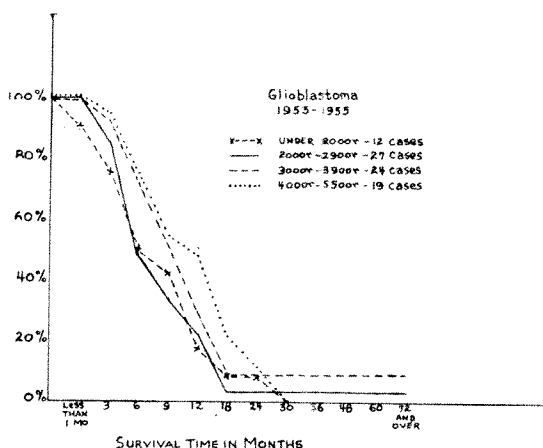


FIG. 6. This series of curves is only for patients treated between 1953 and 1955. At this time a single protracted course of treatment was used in most instances as explained under "Treatment Approach." Those patients receiving a single protracted course of 4,000 to 5,000 r were all dead at thirty months, whereas there were several survivors in the group receiving between 2,000 and 3,900 r, ranging up to six years.

In the entire group of 425 surgically verified cases, only 7 lived five years or longer and only 4 were alive at the time of this study. The dose of radiation did not seem to be a significant factor in the long survival: 2 of these 7 patients received under 2,000 r, 2 received between 2,000 and 3,000 r, and 3 received between 3,000 r and 4,000 r. It is interesting that there are no long term survivals in the group receiving a single protracted series of 4,000 r to 5,500 r (Fig. 6). The one case indicated on the curve of Figure 4 was treated prior to 1953 and consequently received this amount in 3 separate courses of about 1,500 r to 1,800 r each. This may not be statistically significant since only about 20 patients who were seen between 1953 and 1955 were treated with a single protracted course. However, in the same three year period there were 2 cases receiving between 3,000 and 3,900 r, and 1 case receiving between 2,000 and 2,900 r which survived five years (Fig. 6). Further evaluation of these figures with more cases added subsequent to 1955 is necessary and is being carried out at the moment.

SUMMARY

The survival statistics in cases of glioblastoma multiforme here reported are in substantial agreement with those reported by other authors.^{1,2} The three year and five year survival rate was 11 per cent and 7 per cent respectively in the 125 cases reported by Bouchard and Pierce.¹ These figures are somewhat higher than those in our group of cases, but this may be due to the pathologic interpretation. Some pathologists might tend to include a somewhat atypical tumor in the Grade III astrocytoma series when it is actually a Grade II lesion, a more benign type. The reverse may be true in other laboratories. Our Grade III cases had substantially the same survival curve as the cases of "pure" glioblastomas (Fig. 7).

It is apparent that radiotherapy is capable of prolonging life provided that the patient lives for at least thirty days after diagnosis so that the course of treatment can be completed. In order to accomplish this it is necessary to perform a surgical de-

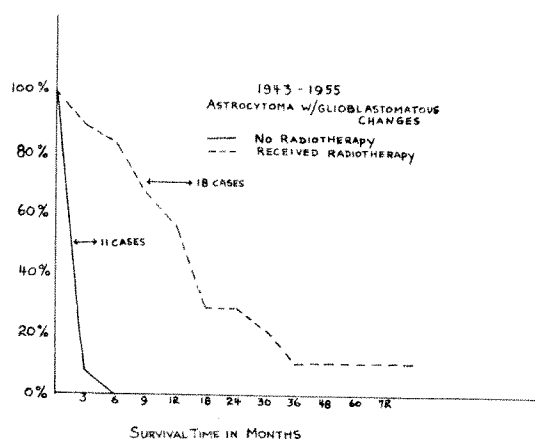


FIG. 7. The curves, which apply to tumors classified as astrocytoma with glioblastomatous changes by our pathologists, demonstrate that the curve in the "surgery only" group is identical to that in the general group seen in Figure 1 (solid line). The only difference between this group and the pure glioblastomas is that at eighteen and twenty-four months there was approximately a 27 per cent survival, whereas in the curve of Figure 5 it is apparent that survival was about 10 per cent at this time. At thirty-six months, however, the figures are quite similar.

compression in a high percentage of cases. A flap should be lifted for as much tumor removal as possible. This can be done without increasing the patient's neurologic deficit, even in vital areas of the brain, provided that the surgical removal is confined to the tumor. Even though survival time is not lengthened (90 per cent are dead in eighteen months), the rapid improvement in symptoms following such surgical intervention is often beneficial in prolonging the patient's useful period of survival.

On the basis of these statistics we advocate adequate surgical decompression, partial or gross total removal of neoplasm, if possible, followed by radiation therapy to be started six or seven days after surgical intervention, or sooner (third day) if needle biopsy only was performed. The dose of radiation in the first three to six days of treatment should be increased gradually until a daily dose is reached sufficient to deliver the prescribed amount of radiation in the optimum time.

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THE RADIUM TREATMENT OF RECURRENT CANCER OF THE UTERINE CERVIX

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IN PUBLISHED reports on the treatment of invasive cancer of the uterine cervix, most authors include all the patients they have seen. Undoubtedly, every large series also comprises some patients with recurrent cervical cancer. By recurrent cancer I mean recurrence of the primary tumor after apparent complete destruction. It is obvious that nearly all "recurrent" cancers are, in reality, persistent cancers and that many "cured" patients probably have viable tumor cells locked in post-therapy fibrosis. Occasionally, several years after apparent complete recovery, a patient will develop regrowth at the site of the primary lesion. Patients who developed metastasis subsequent to destruction of the primary lesion are not included in this series unless the primary growth also recurred.

According to the scanty information in the literature, these patients are usually treated in a palliative way only. Van Herik and Fricke⁴ in 1955 reported a series of 110 cases of recurrent cancer of the female genital tract of which 58 involved the cervix, the vagina or the corpus. In their series they attempted curative therapy whenever possible. Of 5 patients with recurrent tumors involving the cervix or corpus, 3 lived over five years. Two, with recurrences in the vagina only, made complete recoveries. Of 4 cases involving the cervix and the vagina, 2 recovered and 5 of those 47 cases with recurrence involving the cervix, vagina and parametria lived over five years free of disease. The only other article found on this subject is one by Calkins,¹ who reported a similar series of 233 patients requiring retreatment. Most of these recurrences, however, were in sites other than the cervix.

Of about 300 cases diagnosed as invasive

cancer of the cervix and treated in my office between 1933 and 1957, 5 were readmitted later with recurrences of the primary growth. Forty-nine other patients who had recurrent primary lesions after previous treatment elsewhere are also included in this study. All patients had been apparently well for at least three months and 40 for over six months. The purpose of this paper is to report the series of 54 cases and to emphasize that many patients who have recurrences of the primary cervical cancer may be salvaged with individualized radium treatment.

MATERIAL

All patients had recurrent or persistent cancer in the vagina. Many patients demonstrated advanced disease with metastases or with frozen pelves. Two of the patients previously treated by panhysterectomy presented distant metastases.

Since most patients who developed primary cancer of the cervix between 1933 and 1945 were treated with radium or roentgen irradiation, or both, those with recurrent lesions admitted during these years had been treated similarly. Between 1945 and 1957 most of the patients suffering with recurrence of their cervical cancers had been previously treated surgically.

The average time between the first treatment and retreatment of the primary recurrence was 15.8 months and varied from three months to ten years. Of 51 patients whose time interval between the first treatment and retreatment was three years or less, the average was 11.4 months. It was usually difficult to obtain a thorough history of the former treatment but the type of surgery performed was known. For radium therapy usually the "T" type applicator was employed for about three days.

Of the 54 cases, 3.7 per cent were classified as Stage I, 35.1 per cent as Stage II, 37.2 per cent as Stage III, and 24 per cent as Stage IV. Five cases discontinued therapy, 21 were treated for palliation only and 28 were given a full course of treatment as it was believed complete recovery was possible.

TREATMENT

The technique used in my office is quite different from that found in most centers. I feel that the divided dosage has more effect on the tumor and less on the normal tissues in all forms of radiation therapy. With this method it is possible to determine the relative sensitivity of both tumor and normal tissues as the treatment progresses and thus to learn the most effective dose for each individual tumor. All patients are carried as out-patients. Irradiation is started by administering one-half hour daily exposures with a vaginal applicator containing 400 mg. or more of radium.

A long vaginal speculum is inserted and opened as widely as possible. A gold plate 6 mm. in thickness is placed inside the posterior blade beneath the cervix. A plastic ovoid containing the radium tubes is so shaped that the dosage is the same on all its surfaces. The applicator is fixed to the end of a long aluminum rod. For successive treatments it is placed resting on the gold plate against the end of the cervix or in either lateral fornix. If the cervix has been removed, the ovoid is placed in the vault around the growing edge of the recurrent tumor. It is fixed by cotton or gauze packing and a double "T" binder holds the speculum and applicator firmly in place throughout the duration of the short treatment. The gold plate protects the rectum. The widely opened speculum also aids in protection by forcing the bladder and rectum away from the applicator. Seldom does frequency of urination or diarrhea appear and serious damage to the bladder, ureters, or rectum almost never occurs. External

therapy is utilized only in patients with advanced disease.

All cases are individually evaluated. The persistent tumor tissue is adequately irradiated. If the patients have been previously treated with radium, they are re-treated with caution. The dosage is carried to the tolerance of the normal tissues. The same general rule is utilized in recurrences which follow surgery. An average dose to Point "A" is 8,000 to 10,000 gamma roentgens over a four to six week period.

If the uterus is still present and if the cervical canal can be found, about one-third of the dose is delivered by means of a slender intrauterine applicator. This applicator is only inserted after the vaginal treatment has been completed and no tumor is present in the cervical canal when it may be introduced without traumatic dilatation. Additional radium bomb or roentgen-ray treatments are administered over the lateral pelvic areas in Stage III and IV patients.

At the Radiumhemmet in Sweden, long known for its efficiency in the treatment of cervical cancer, a routine technique of radium therapy has been discontinued and now each case is considered individually. In my experience, no 2 patients are alike in their anatomic structure, their reaction to irradiation or in the extent of their tumors. Thus, it is necessary to modify the technique with each patient.

HISTORIC DATA

Figure 1 shows the age distribution of the patients. The largest number of patients was found in the fifty-one to sixty-five year age groups: 7 in the fifty-one to fifty-five year, 10 in the fifty-six to sixty year group, and 9 in the sixty-one to sixty-five year age bracket. The youngest patient was twenty-eight years and the oldest patient sixty-nine years of age. The average age was 50.5 years.

Fifty of the patients were married or widowed. Children were born to 67.7 per cent; of these 20.5 per cent had 1 child,

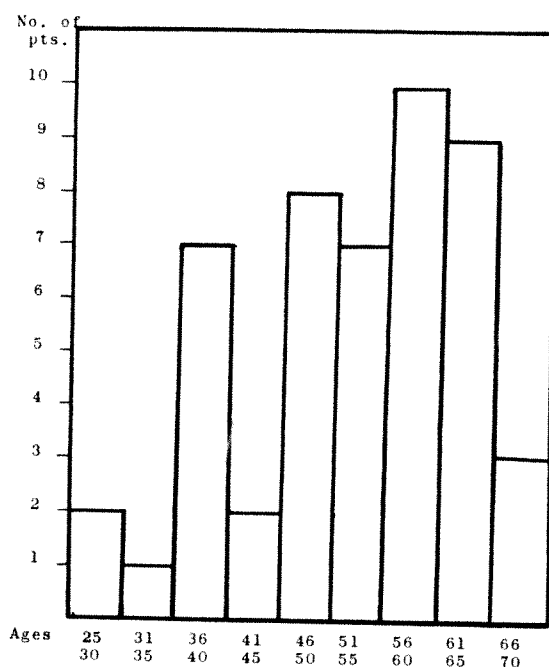


FIG. 1. Age distribution of patients in reported series (age unknown in 5 patients).

29.4 per cent had 2 children and 17.8 per cent had from 3 to 10 offspring.

It was difficult to obtain information regarding the exact duration of symptoms before the patients had their surgery or first radiation therapy. The time recorded varied from two weeks to three years: 47.6 per cent went to their family physicians within three months after their first symptoms; 21 per cent between 3 and 6 months; 23 per cent between 6 months and one year; and 8.4 per cent between one and three years. The average length of time from beginning of symptoms until they saw their family doctors was 6.5 months. As these periods of delay are somewhat shorter than usual in a series of cervical cancer, they are suggestive that on the whole these patients, when first seen, were in the early stages of the disease. This conclusion is reasonable as many of the patients were initially operated upon and few surgeons would attempt definitive surgery in any but an early case. The clinical data before admittance to my office are quite different. None of the patients reported

had been ill less than five months. Ten, or 18.6 per cent, came between five and six months after their first symptoms; 15, or 27.6 per cent, had had symptoms from six months to twelve months; 18, or 33.2 per cent, from 1 to 2 years; and 11, or 20.6 per cent, over 2 years. The average duration of illness was 21.6 months.

Vaginal discharge was a complaint in 92.5 per cent of the patients in this series, and 90.7 per cent complained of bleeding. Pain was a symptom in 35.1 per cent, but only in patients with advanced disease. The recurrent vaginal tumor varied in size from 1 cm. to 15 cm. in greatest diameter. Two patients had lesions of 1 cm. in diameter, 5 of 2 cm., 15 of 3 cm., 9 of 4 cm., 6 of 5 cm., 6 of 6 cm., and 9 had lesions of 7 cm. in diameter or larger. The average greatest diameter of all lesions was 4.6 cm. The exact diameter of 3 cases was not recorded.

Ulceration was present in 47, or 87 per cent, and in 41 the tumor was friable. The entire vaginal wall was involved in 4; the superior three-quarters in 5; one-half of the canal in 17; and the vault alone in 18 patients. The tumor mass was completely fixed in 13, and partially fixed in 17 patients. The urinary bladder was invaded in 3 patients. Distant metastases had occurred in 2 patients. Parametrial involvement was found in 40, or 74 per cent.

RESULTS

Table I gives the type of previous treatment of the entire series of patients and the end result after retreatment.

Seven patients had been first treated by cautery. It is assumed that these were patients in whom the physician mistook an early invasive cancer for chronic endocervicitis. Of 3 patients who had had only cauterization, 2 were referred after six and nine months (Stages II and III) and eventually made complete recoveries. One, referred after a delay of one year (Stage II) may have recovered but was lost to follow up after eight months. Of the 4 remaining patients who were first cauterized, 1 w

TABLE I
TYPE OF PREVIOUS TREATMENT AND RESULTS AFTER RETREATMENT WITH RADIUM

Patient	Previous Treatment		Time Lapse since First Therapy	Stage	Results					
	Primary	Additional			Discontinued Treatment	Lost to Follow-Up	Living with Cancer 3 Yr.	Dead of Disease	Living and Well 3 yr.	Living and Well 5 yr.
1. SO	Cautery	Amputation of cervix Roentgen-ray Roentgen-ray Radium	6 mo.	II						x
2. SC	Cautery		9 mo.	III						x
3. HU	Cautery		1 yr.	II		x				
4. LA	Cautery		5 mo.	I				x		
5. FE	Cautery		3 mo.	IV				x		
6. MA	Cautery		1 yr.	III						x
7. SW	Cautery		2 yr.	IV				x		
8. WA	Amputation of cervix		4 mo.	II						x
9. HA	Amputation of cervix		1 yr.	II	x					
10. BA	Supravaginal Hysterectomy	Cautery	6 mo.	II				x		
11. SW	Supravaginal Hysterectomy	Cautery	10 mo.	II						x
12. RU	Supravaginal Hysterectomy	Radium	17 mo.	III						x
13. PA	Supravaginal Hysterectomy	Radium Roentgen-ray+roentgen-ray+ra	5 mo.	II		x				
14. KE	Ra+panhysterectomy		1 yr.	IV				x		
15. ST	Ra+roentgen-ray and panhysterectomy		14 mo.	III				x		
16. RO	Panhysterectomy		1 yr.	III				x		
17. DI	Panhysterectomy		2½ yr.	III				x		
18. MA	Panhysterectomy		2 yr.	IV					x	
19. ST	Panhysterectomy		6 yr.	IV			x			
20. TA	Panhysterectomy		28 mo.	III	x					
21. PE	Panhysterectomy		1 yr.	IV				x		
22. SI	Panhysterectomy		6 mo.	IV				x		
23. EL	Panhysterectomy		1 yr.	IV				x		
24. MC	Panhysterectomy		11 mo.	IV				x		
25. CA	Panhysterectomy		7 mo.	III				x		
26. MC	Panhysterectomy	Roentgen-ray	3 mo.	II						x
27. TU	Panhysterectomy		4 mo.	II						x
28. SW	Panhysterectomy		21 mo.	II						x
29. JA	Roentgen-ray		3 mo.	III				x		
30. HO	Roentgen-ray		1 yr.	II					x	
31. MC	Ra		3 mo.	II				x		
32. GR	Ra		7 mo.	II				x		
33. KE	Ra		18 mo.	III			x			
34. ST	Ra		21 mo.	II					x	
35. WO	Ra		22 mo.	III			x			

TABLE I (Continued)

Patient	Previous Treatment		Time Lapse since First Therapy	Stage	Results					
	Primary	Additional			Discontinued Treatment	Lost to Follow-Up	Living with Cancer 3 Yr.	Dead of Disease	Living and Well 3 yr.	Living and Well 5 yr.
36. FA	Ra		7 yr.	IV	x					
37. TA	Ra		4 mo.	IV	x					
38. BR	Ra		6 mo.	III				x		
39. RE	Ra		6 mo.	IV				x		
40. CI	Ra		1 yr.	IV				x		
41. RO	Ra		4 mo.	III				x		
42. GA	Ra		7 mo.	II			x			
43. HA	Ra		1 yr.	II					x	
44. WA	Ra		10 yr.	I					x	
45. SM	Ra		6 mo.	III					x	
46. JO	Ra+roentgen-ray		5 mo.	III				x		
47. CA	Ra+roentgen-ray		5 mo.	II				x		
48. DE	Ra+roentgen-ray		5 mo.	III				x		
49. SC	Ra+roentgen-ray		9 mo.	III				x		
50. AL	Ra+roentgen-ray		5 mo.	II				x		
51. LI	Ra+roentgen-ray		29 mo.	III				x		
52. DR	Ra+roentgen-ray		8 mo.	III				x		
53. NO	Ra+roentgen-ray		1 yr.	II	x					
54. LO	Ra+roentgen-ray		9 mo.	III				x		

further treated by cervical amputation while pregnant and five months later was referred to my office (Stage I). She died of her disease after eighteen months. Two patients were treated with additional roentgen irradiation after cauterization. One was referred after three months (Stage IV) and died of her disease two years after radium treatment. The other patient, referred one year after cautery and roentgen therapy (Stage III), completely recovered. The seventh patient whose initial treatment was cauterization also had been given radium therapy and was referred two years later for palliative radium therapy (Stage IV). She died after three months.

Amputation of the cervix was the primary treatment administered to 2 pa-

tients. One of these, referred after four months (Stage II), made a complete recovery. The other patient, who received radium therapy and was referred after one year (Stage II), refused to complete her course of treatment and died of disease after two years.

Supravaginal hysterectomy for bleeding was the primary treatment in 4 patients. Two had additional cauterization of the cervix. One of these, referred after six months (Stage II), died of disease two years after retreatment with radium, and the other patient, referred after ten months (Stage II), made a complete recovery after treatment for the recurrence. Following supravaginal hysterectomy, a third patient received radium therapy. After 17 months

(Stage III) she was referred to me and made a complete recovery after retreatment with radium. The fourth patient who had had a supravaginal hysterectomy was given roentgen therapy immediately, followed by a second course of radium and roentgen therapy. Five months later (Stage II), she responded well to additional radium therapy administered in my office and was lost to follow-up after eighteen months. At this time she was apparently free from disease.

Two patients were irradiated first and then subjected to panhysterectomies. One of these received both radium and roentgen irradiation and 1 had radium therapy alone before operation. Both were referred to me about one year later (Stages III and IV), and both died of disease within six months after retreatment.

Thirteen patients were first treated by panhysterectomies. Few, if any, had lymph node dissections. It is of interest that 2 had evidence of distant metastasis in addition to vaginal recurrence when seen in my office. Four of these patients had a course of roentgen therapy postoperatively. One, referred after 1 year (Stage III), died of disease two years after retreatment. One, referred after two and one-half years (Stage III), died of disease fourteen months after retreatment. Of the remaining 2 patients, 1 was referred after two years (Stage IV) and made a complete recovery after retreatment. The other patient, referred after six years (Stage IV), lived with disease for four more years. Of the remaining patients whose original treatment consisted of panhysterectomy, 1, referred after twenty-eight months (Stage III), discontinued treatment; 5, referred from six months to one year after operation (4, Stage IV, 1, Stage III), died from three months to two years after retreatment. The remaining 3 patients, referred three, four and twenty-one months following operation (all Stage II), recovered completely and are alive after twenty years, nine years and six years, respectively.

One patient, who had received one course of roentgen therapy was referred to me

three months later (Stage III), and died five months after retreatment. One patient, given two courses of roentgen-ray therapy, referred after one year (Stage II), is living and free of disease four years after retreatment.

Radium therapy alone was administered primarily in 15 patients, 5 of whom were first treated by me. These 5 were vigorously treated. Recurrence was noted three months, seven months, eighteen months, twenty-one months and twenty-two months, respectively, after completion of their first course of treatment. One patient (Stage II) is living and well four years after the second course of therapy. The 4 remaining patients have succumbed to their disease; 2 after two years (Stage II) and 2 after three years (Stage III). Of the 10 patients receiving their initial radium treatment elsewhere, 2 discontinued treatment (Stage IV); of 4 patients (2, Stage III, 2, Stage IV), referred before one year had elapsed, all died of disease between three and five months. These patients had advanced disease and were treated with radium for palliation only. One patient, referred after seven months (Stage II), lived 3 years with cancer. One patient, referred after one year (Stage II), was living and well three years later. One patient, referred ten years after her original treatment (Stage I), was alive and well four years later and was burned to death in a fire. One patient, referred after six months (Stage III), is well eleven years after treatment of her recurrence.

Radium and roentgen therapy were the primary treatments for 9 patients. Six patients, referred from five to twenty-nine months after their first treatment (4, Stage III, 2, Stage II), died of cancer from seven months to two years after retreatment with radium. Four of these patients received palliative therapy only. The remaining 3 patients who received radium and roentgen-ray therapy primarily had also received additional roentgen-ray therapy and were referred to me eight months to one year later. One of these patients

TABLE II
THREE YEAR RESULTS

Total Cases	54	
<i>Indeterminate Cases</i>		
Discontinued Treatment	5	
Lost To Follow-Up	2	
	7	
<i>Determinate Cases</i>		
Living and Well	15	(31.9%)
Dead of Disease	28	(59.6%)
Living with Cancer	4	(8.5%)
	47	(100.0%)
FIVE YEAR RESULTS		
Total Cases	51	
<i>Indeterminate Cases</i>		
Discontinued Treatment	5	
Lost To Follow-Up	4	
Dead of other Disease	2	
	11	
<i>Determinate Cases</i>		
Living and Well	10	(25%)
Dead of Disease	30	(75%)
	40	(100%)

(Stage II) discontinued treatment and the remaining 2 patients (Stage III), given palliative therapy only, died of their disease four and ten months later.

Table II gives the results of treatment of all 54 patients who had recurrent cancer of the uterine cervix. The three year results show that in the indeterminate group are 7 patients; 2 were lost to follow-up and 5 discontinued treatment. In the determinate group of 47 cases, 28 died of cancer in less than three years; 4 lived with cancer three years or over; and 15, or 31.9 per cent were apparently free from disease. Of 40 cases (determinate) in the five year group, 30 died of disease and 10, or 25 per cent were alive and free of disease.

DISCUSSION

Paterson² states, "When local recurrence follows operative treatment, a single ovoid or thick sorbo tubing with central radium in the vagina will relieve the local symp-

toms, but only palliation is to be expected. When recurrence follows a full course of radiation therapy, treatment can only be directed to the relief of pain." It is probable that the recurrent cervical cancer cases seen by Paterson had previously been subjected to more radical treatment than had the average patient in this series.

The preliminary treatment of many of the reported cases indicates the necessity of making a diagnosis before therapy is undertaken. It is assumed that those patients treated by supravaginal hysterectomy, Sturmdorf operation, or simple cauterization were treated under mistaken diagnoses. It is also possible that the forceful insertion of a "T" type radium applicator and the administration of a predetermined dose in three days is to invite failure through traumatic spread of the growth or through inadequate or excessive dosage.

In recent years the popular trend toward simple hysterectomy has resulted in an increasing number of recurrent lesions. It is difficult to understand why surgery is so frequently used in this country in Stage I and II cancer of the cervix, while for the most part elsewhere in the world radium therapy alone is employed. A forceful editorial by Reis³ emphasizes that cancer of the cervix is not a surgical disease. His logic is sound and reasonable. What statistics are available show that properly applied radium therapy results in a much higher percentage of cures than surgery. Functional anatomy is also preserved.

Many authors recently have made the observation that tumor cells are often transplanted by means of suture thread and they have stressed the frequent finding of free tumor cells in the operative field. The frequency of recurrence and of bizarre distant metastasis following surgery indicates that the cancer surgeon should be specially trained in the pathology of cancer.

Recurrence after irradiation has usually occurred when a "T" type applicator has been used in a "routine" manner for three days. Because all patients are different and no two tumors are alike, individualization

of the patients and the divided dose technique are necessary in the treatment of cervical cancer. This is substantiated by the results obtained in the present series; there was a five year cure rate in determinate cases of 25 per cent in patients with recurrence of the primary cervical cancer.

SUMMARY

Of about 300 patients treated for cancer of the cervix uteri, 54 had recurrent lesions. These cases were treated three months to seven years previously. Many also had metastases or extensive pelvic involvement.

In the three year group, 21 patients were given palliative treatment only, while 28 received a complete course of radium therapy. Five patients discontinued therapy. Two patients were lost to follow-up. Of the remaining 47 cases, 15, or 31.9 per cent, made a three year clinical recovery. Of 40 determinate patients in the five year group,

10 or 25 per cent, recovered.

It is evident that an appreciable number of patients with recurrent or persistent cervical cancer after definitive treatment may be salvaged with individualized radium therapy, if the tumor is still confined to the vagina or adjacent structures.

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COMPARATIVE STUDY OF SUPERVOLTAGE RADIOTHERAPY TECHNIQUES IN SOME PELVIC MALIGNANCIES*

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THE first supervoltage equipment in Mexico was installed in July, 1956, at the Radiotherapy Department of the National Cancer Institute in Mexico City. It was a theratron junior unit with 600 curies, the only source available for us at that time. Soon after, another hectocurie unit, a Keleket Barnes, was available for our work in another clinic. It was planned to use this equipment mainly for the treatment of carcinoma of the cervix, the prevalent malignant neoplastic disease in Mexico.

It was decided at that time to treat this malignancy along three main lines: (1) Carrying on as before, treating the primary lesion by radium and using supervoltage external irradiation exclusively for the treatment of the parametria and the pelvic lymph node chains; (2) irradiating the whole pelvis by external irradiation only; and (3) using external irradiation of the whole pelvis followed by local supplementary radium treatments at lower dosage, or transvaginal roentgen therapy or a concentration of an extra dose by the small volume rotational technique.

For the past four and a half years, a total of 802 patients with carcinoma of the cervix has been treated along these lines, predominantly the first, with the hectocurie Co⁶⁰ units.

Two years ago, a new Radiotherapy Department at the Mexico City Medical Center was equipped with three large telecobalt units and a 15 mev. betatron for electron and roentgen-ray therapy. It was then decided to make a comparative study of some of the current radiotherapy tech-

niques employing external irradiation in carcinoma of the cervix, bladder and ovary. To study depth dose distribution, a survey was made by ionometric, computational, photodensitometric, and clinical measurements. The aim was to find the most suitable technique for the individual patient from the physical and clinical points of view, making at the same time the necessary comparisons with our technique at 200 kv. and the previous experience with the hectocurie telecobalt units.

EQUIPMENT

The equipment in this survey consisted of two Siemens gammatrons, each loaded with a 1,600 curie Co⁶⁰ source for pendular, tangential rotation and static techniques; a theratron senior with a 2,000 curie Co⁶⁰ source, and a 15 mev. Siemens betatron for stationary, pendular and tangential rotation with roentgen rays or electron beam.

We used a "Simplex" dosimeter with standard and intracavitary micro chambers, with accuracy up to 1/10th of r for dose rate and integral measurements. Comparative measurements were undertaken with the Siemens and Philips universal dosimeters. A Victoreen with 25, 100 and 200 r chambers was kept as a standard against the U.S.A. National Bureau of Standards measurements, calibrated through the Physics Laboratory of the M. D. Anderson Hospital, Houston, Texas.

The roentgen was kept as a unit of exposure and the rad to express tissue dosage only. With energies up to 250 kv., measurements were taken in roentgens with the standard ionization chambers. A 4 mm.

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lucite cap was used for cobalt 60 and for the betatron roentgen ray beam; the chamber was mounted in the center of an amber cylinder 7 cm. in diameter. The term "nominal r" was adopted in the Department for these last two levels of energy.

We had a plexiglas water phantom with an oval shaped transverse section 20×30 cm. with a special device to introduce ionization chambers and locate their position in two planes, to check calculated distributions in some moving field techniques. A semi-automatic water phantom was employed to elaborate some isodose curves for the gammatrons. Photodensitometric studies were made in a presswood phantom with oval shaped slabs 2 cm. thick and 20×30 cm. in diameters. Also, a sectional paraffin wax phantom with pelvic bones included and outlined with lead wire was used to take radiographs for some moving field techniques at 250 kv. and Co^{60} .

Depth dose distributions for the theatron were worked out using the isodose curves provided by the Canadian Atomic Energy Commission. The computational methods for moving field therapy were based on the well-known procedures of Braestrup and Mooney,⁵ and of Johns and his colleagues.^{13,14}

To spare the use of the betatron doughnut in ionometric measurements, a wide use of film dosimetry was planned. Type M Kodak industrial film was chosen and a complete logarithmic characteristic curve of sensitivity was made for each lot. Rigid constant darkroom conditions were kept throughout this work. A very sensitive photodensitometer mounted on a special home-made view box proved to be a most reliable and useful tool for this purpose.

CARCINOMA OF THE CERVIX

PARAMETRIAL TECHNIQUE WITH STATIC FIELDS

In Stage I and II cases in which intracavitary radium application is contemplated, the external irradiation should be planned to cover the lateral aspects of the parametria, the uterosacral ligaments, the obturator, external iliac, hypogastric, pre-

sacral and common iliac lymph nodes.

In patients with anteroposterior diameters less than 19 cm., two opposing portals, 15 cm. wide and 12 to 14 cm. high, with a center lead block so as to produce geometric screening 4 cm. wide at the mid-pelvis, could be used to deliver one-hundred per cent with Co^{60} at the level of the parametria. In this way, however, there is always an undesirable overloading of the subcutaneous tissue. The same results can be obtained with the use of two pairs of opposing fields, 6×14 cm., 2 cm. off the middle line. Figure 1 shows the radiograph (*A*) obtained and the depth dose distribution (*D*) for Co^{60} teletherapy at 75 source skin distance for two pairs of opposing fields. In thin patients, these two fields give a good depth dose, but there is always an overloading of the subcutaneous tissue. To avoid this, it is preferable to use three parametrial portals, an anterior, a sacral, and a gluteal field, 10×6 cm. (*E*). A hot spot with the highest depth dose is formed at the level of the uterosacral ligament, so often involved in late Stage II and III cases. A good covering of the parametria and main lymph node chains is achieved within the 80 to 90 per cent curves of the maximum depth dose. On the other hand, the overloading of the anterior field produces a forward displacement of the hot spot, if desired, toward the mid-pelvis. A betatron beam gives a well limited volume of radiation with no side scatter and no contribution to the center of the pelvis (*B*). The 200 kv. radiation with the same technique produces a very wide beam in the depth with a high contribution to the center and a poorly limited volume of radiation with diffuse scatter resulting in a foggy appearance of the whole radiograph (*C*).

Figure 1 *F* illustrates measurements in a phantom 20×30 cm., showing the greater depth dose, the larger volume of homogeneous irradiation and the diminished irradiation of the subcutaneous tissue with the increase of the energy from 200 kv. to Co^{60} and 15 mev. when two opposing fields are used. The doses are expressed as 100

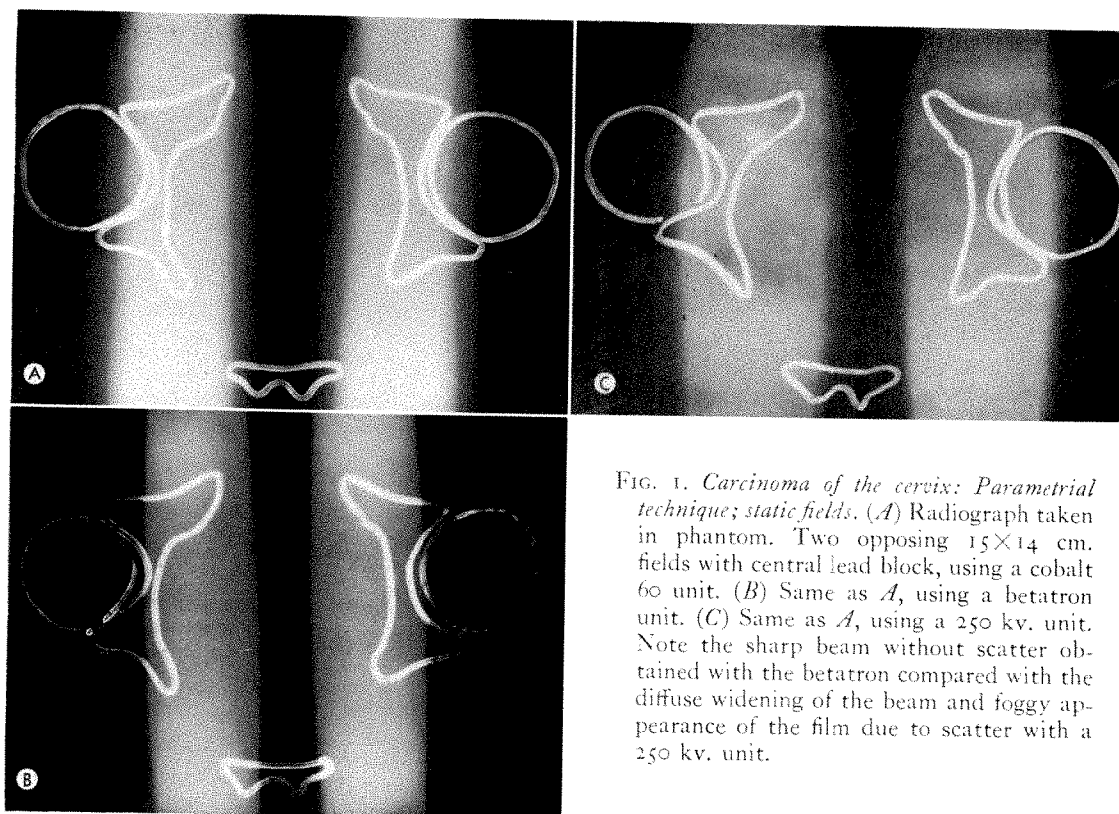


FIG. 1. *Carcinoma of the cervix: Parametrial technique; static fields.* (A) Radiograph taken in phantom. Two opposing 15×14 cm. fields with central lead block, using a cobalt 60 unit. (B) Same as A, using a betatron unit. (C) Same as A, using a 250 kv. unit. Note the sharp beam without scatter obtained with the betatron compared with the diffuse widening of the beam and foggy appearance of the film due to scatter with a 250 kv. unit.

nominal roentgens given to each of the opposing fields.

PARAMETRIAL TECHNIQUE WITH ROTATION THERAPY

Rotation therapy at 250 kv. can produce a very high depth dose at the parametrial level but it is a poor cancer coverage technique. Several years ago, the Becker arrangement of two lateral convergent pendulations plus perineal pendulation, using the Müller T U. 1 250 kv. machine, was studied in our department. A good depth dose was obtained in the parametria but the lymph node areas were not sufficiently irradiated. With supervoltage, even higher depth dose could be delivered by simple 110° or 120° lateral pendulation. Film dosimetry and phantom measurements showed again the poor covering of the lymph node bearing areas and also a high contribution to the mid-pelvis. Thus, moving field techniques for parametrial irradiation were not considered useful in this survey.

With moving field techniques, we were able to produce an interesting distribution obtained only with high energy radiation and at its best with the betatron with energies above 10 mev. This is shown in Figure 2 and we call it "internal tangential rotation." It is produced with 150° and 170° anterolateral pendulation, with a 15° tilting off the axis of rotation and centered at 4 or 5 cm. out of the mid-line in the posterior third of the parametria. We have not been able yet to find a computational method to calculate the depth dose. It should be further studied since it permits a very high concentration of radiation in the depth, covering satisfactorily the lymph nodes in the anteroposterior directions, with full irradiation of the lateral aspects of the parametria, thus complementing the lateral spread of radiation given by intracavitary radium.

WHOLE PELVIS IRRADIATION

Two-field arrangement. The simplest ar-

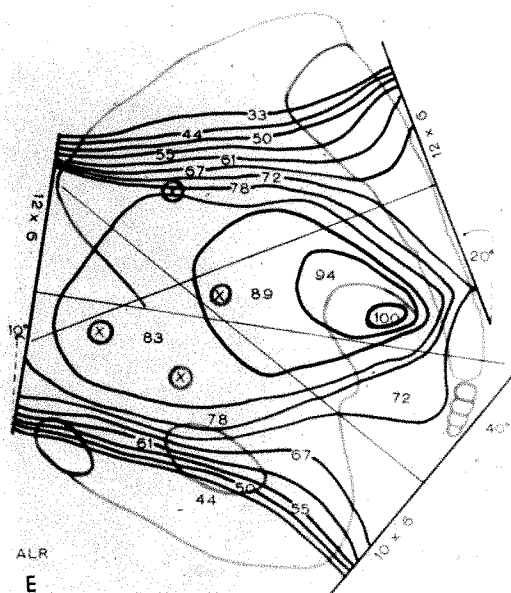
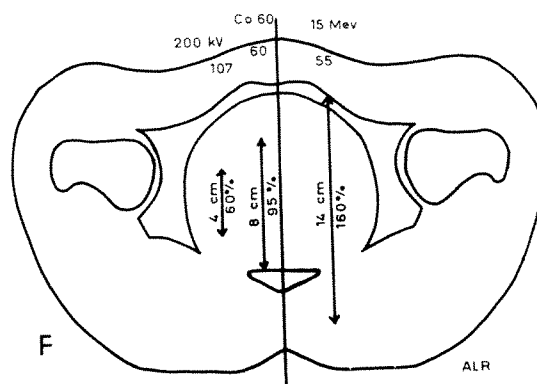
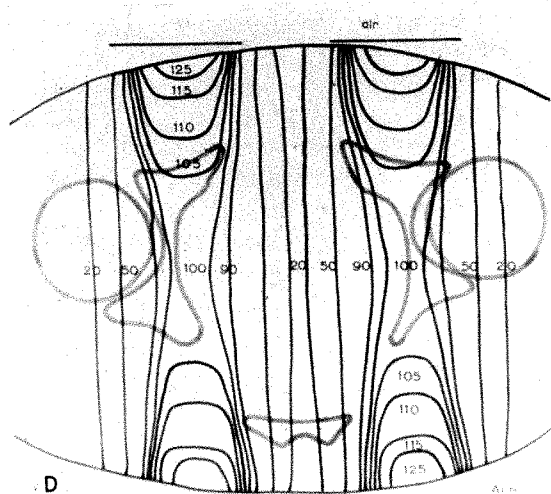


FIG. 1. Carcinoma of the cervix: Parametrial technique; static fields. (D) Depth dose distribution with two opposing 6×14 cm. fields showing the overloading of the subcutaneous tissue, with a Co^{60} unit at 75 cm. source skin distance. (E) Depth dose distribution in the three-field technique with a Co^{60} unit at 75 source skin distance. Anterior, sacral and gluteal fields. The crosses mark the main lymph node areas. (F) Diagram comparing depth dose with 250 kv., Co^{60} and betatron units. The distance between the tips of the arrows is the volume of homogeneous irradiation with two opposing parallel fields. One hundred "nominal r" to each of the fields.

rangement is the use of two opposing fields, 14×12 cm. or 15×12 cm., over the pelvic contents. In this way, it is possible to deliver a high dose to the depth but a high over-dosage of subcutaneous tissue is produced, particularly in the case of Co^{60} (Fig. 3, A and D). This situation is improved with the betatron, due to the depth at which electronic build-up is produced. Also, the volume of tissue receiving homogeneous irradiation is larger. On the other hand, the larger this volume, the greater the amount of intestine irradiated. It is a useful technique for simple palliation in

very advanced cases and it could be supplemented by small amounts of intracavitary radium, or rotational small volume concentrations in the mid-pelvis.

Three-field arrangement. The next step was to survey the techniques using three fields to cover the whole of the pelvis. The results are shown in Figure 3, B and E. For this three-field technique, it was found that the Co^{60} unit produces a better distribution than the betatron because the exit dose is lower. Most of the studies were done at this level of energy at 75 source skin distance with the theratron and the gammatrons. A

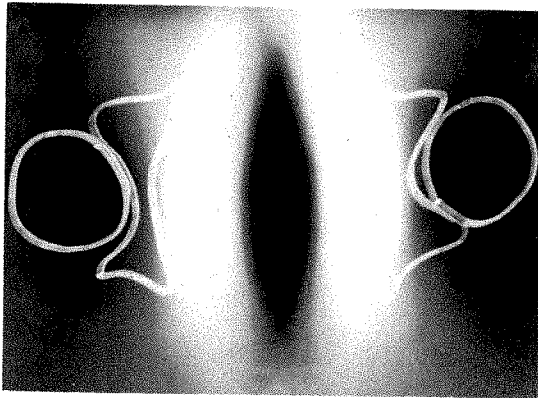


FIG. 2. *Carcinoma of the cervix: Parametrial technique; internal tangential rotation with 15 mev. betatron unit.* This is obtained with a 0 to 150° anterolateral pendulation with a 15° tilting off the axis of rotation.

good distribution is obtained with this approach using fields in a "Y" arrangement, and it is possible to deliver 6,000 to 6,500 rads within six to seven weeks. We have not been able to do it in a shorter time, due to the severe rectal reactions.

A variety of the three-field technique with a telecobalt machine can be used for early cases of carcinoma of the cervix with exophytic tumors. In these cases, it is convenient to treat the primary lesion by external radiation in order to diminish the tumor mass and to permit a better geometric radium application. Pre-radium arrangements with three fields: one anterior, with a lead block in the middle to produce screening of 4 to 4.5 cm. in the depth and two posterior ones converging toward the center give a good distribution (Fig. 3, C and F). Sixty per cent of the maximum depth dose is delivered at mid-pelvis while the parametria receive a homogeneous irradiation with the maximal depth dose. When 1,000 or 1,500 rads have been given to the primary tumor, intracavitary radium application is carried out followed by the standard three-field parametrial technique described above. The advantage of this arrangement is that the over-all time is kept easily within a six week period since

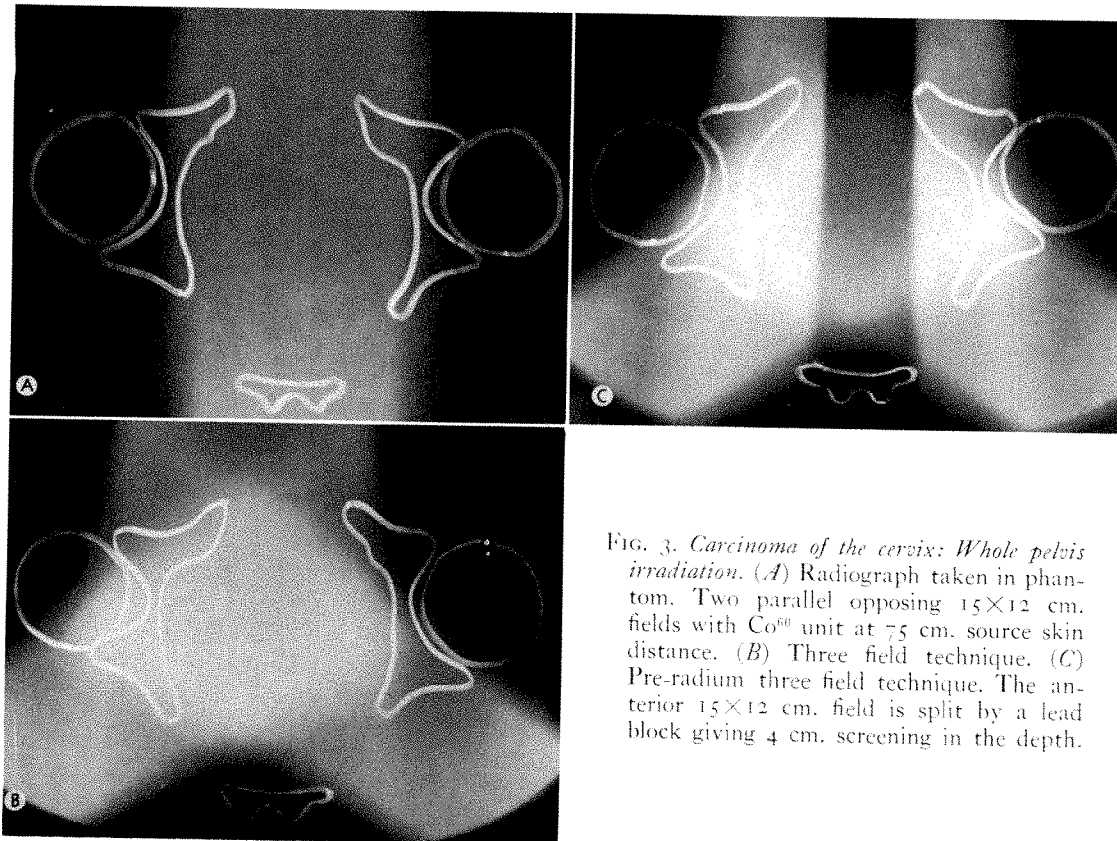


FIG. 3. *Carcinoma of the cervix: Whole pelvis irradiation.* (A) Radiograph taken in phantom. Two parallel opposing 15×12 cm. fields with Co⁶⁰ unit at 75 cm. source skin distance. (B) Three field technique. (C) Pre-radium three field technique. The anterior 15×12 cm. field is split by a lead block giving 4 cm. screening in the depth.

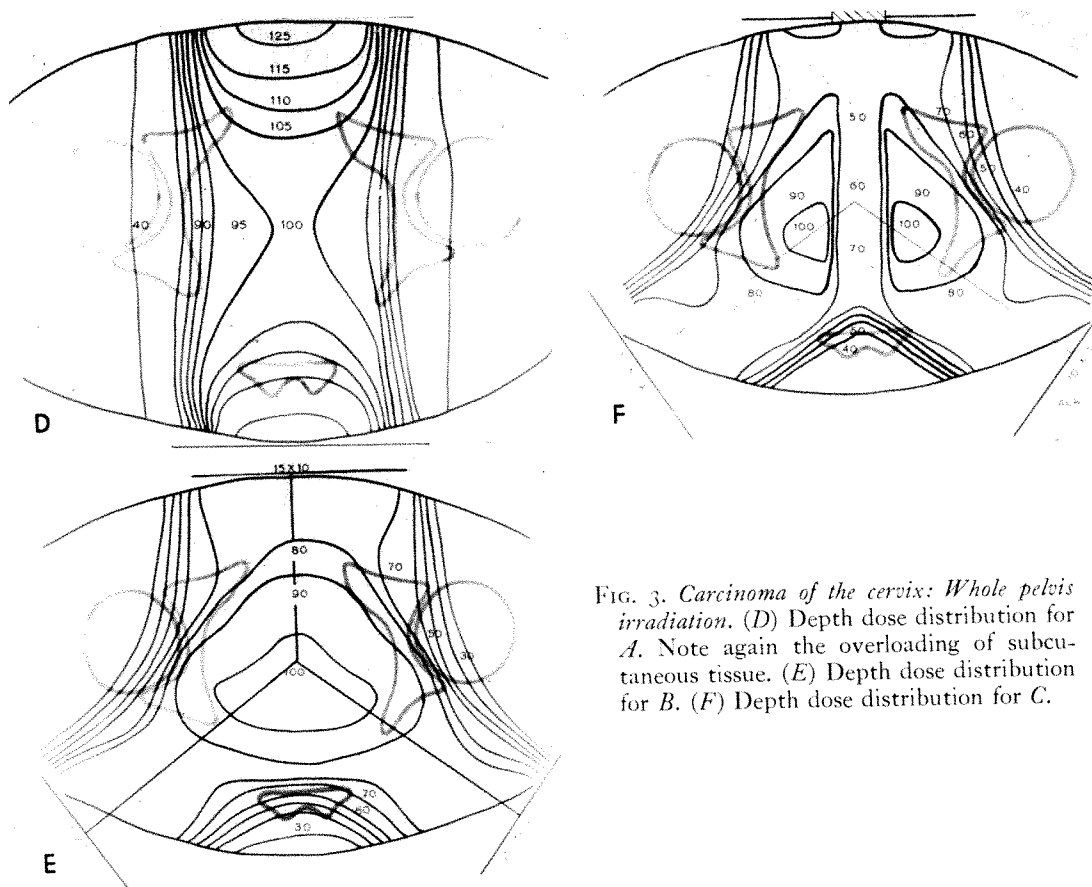


FIG. 3. Carcinoma of the cervix: Whole pelvis irradiation. (D) Depth dose distribution for A. Note again the overloading of subcutaneous tissue. (E) Depth dose distribution for B. (F) Depth dose distribution for C.

the parametria are irradiated simultaneously with the primary tumor, prior to the radium application. In our hectocurie therapy experience, it has proved to be a useful procedure.

Four-field arrangement. The results obtained with the possible arrangements using four static fields can be seen in Figure 4, A-F. Portals 10×14 cm. or 10×12 cm., centered in mid-pelvis at 45° , allow the delivery of a high dose to a great volume in a much better fashion than with 200 kv. This procedure allows a homogeneous irradiation of the whole pelvis and of part of the abdominal cavity, limited only by the tolerance of the intestine and bladder, which are included in the volume of high dosage. It is indeed the classic technique for the treatment of ovarian tumors when the Manchester bridge or strip techniques are not used. At the 15 mev. level, the volume obtained in this arrangement is more precisely limited with no side

scatter, a much higher percentage delivered to the depth and less integral doses, as can be seen on the illustrations.

If the four portals are used at 90° to each other, a better clinical distribution is obtained since the lateral portals can be limited in the anteroposterior direction to 8 or 10 cm., thus reducing the dose to the bladder and rectum. It is the "box" technique described by Fletcher and his group^{6,7} in Houston, and also used by Watson and his colleagues²² in Canada. It seems to be the most desirable arrangement with the betatron in spite of the irradiation of the femur by the lateral fields. Figure 4, C and D shows the difference between Co^{60} and betatron radiation on radiographs taken in phantoms. The depth dose distribution for the 22 mev. betatron has been well studied by the Houston and the Saskatoon groups.

Five-field arrangements. Five-field techniques were studied using three anterior

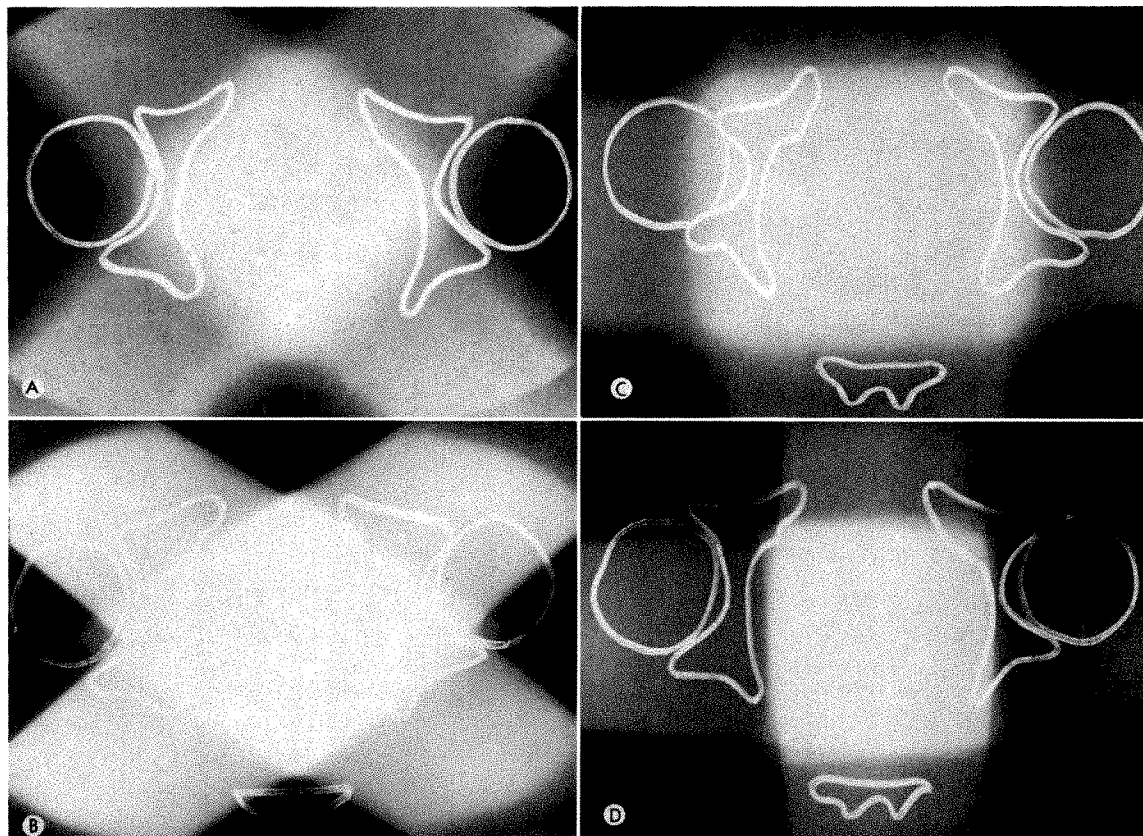


FIG. 4. *Carcinoma of the cervix: Whole pelvis irradiation with four fields.* (A) Radiograph taken in phantom. Four 10×14 cm. fields at 45° to each other and at 75 cm. source skin distance, centered, using a cobalt 60 unit. (B) Same as A using a betatron unit. Very sharply limited volume of radiation. The rectum and bladder are included in the high dose volume of irradiation. Inclination of 35° . (C) "Box" technique with two pairs of parallel-opposed portals at 90° to each other and at 75 cm. source skin distance for a Co^{60} unit. (D) Same for a betatron unit.

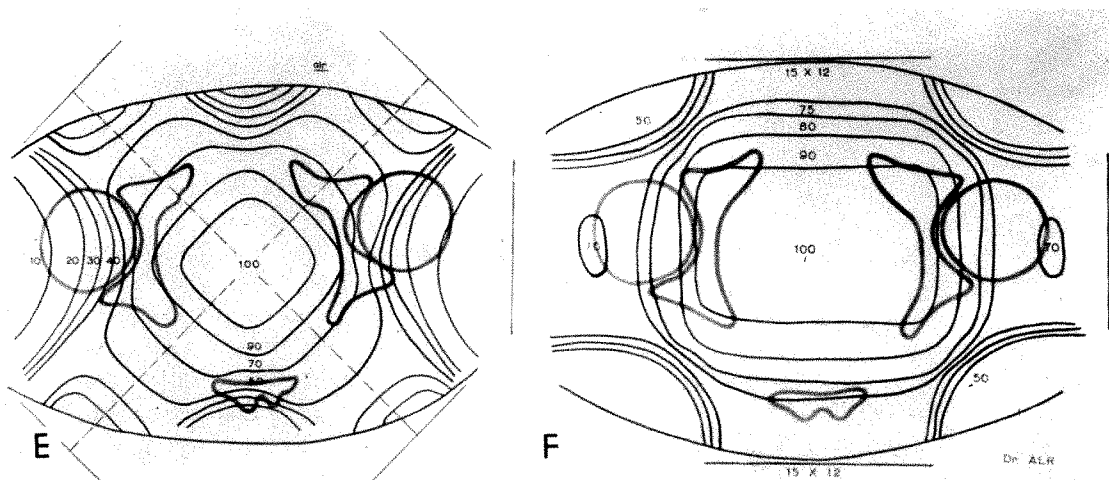


FIG. 4. *Carcinoma of the cervix: Whole pelvis irradiation with four fields.* (E) Depth dose distribution with Co^{60} arrangement shown in A. (F) Depth dose distribution with Co^{60} arrangement shown in C.

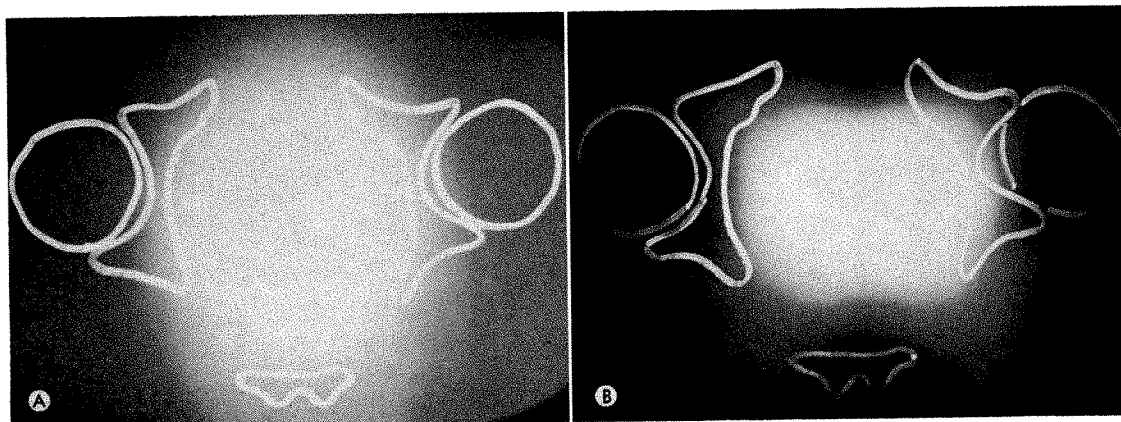


FIG. 5. Carcinoma of the cervix: Whole pelvis irradiation with moving field technique. (A) Radiograph taken in phantom. Full rotation with 10×12 cm. portal and 75 cm. to center of rotation using Co^{60} unit. (B) Radiograph taken with bi-axial lateral 160° pendulation, centered 2 cm. off the mid-line; fields 6×12 cm. A flattening of the volume of irradiation in the anteroposterior direction diminishes the bladder and rectum dose. Shutting off the beam while passing over the femora reduces the dose to these structures.

6×12 cm. portals centered in mid-pelvis and two posterior portals 10×14 cm. It was used by us with 250 kv. to build up enough depth dose in the treatment of very advanced Stage IV cases. With Co^{60} and the betatron units that need does not exist. Besides, an undesirable depth dose distribution, elongated in the anteroposterior direction, was found in this study, ruling out its use.

Full rotation therapy. Some moving field techniques were studied in an effort to diminish the radiation dose to the femur produced by the static field arrangements previously mentioned. The use of full rotation has been proposed by Friedman *et al.*⁸ with 2 mev. roentgen rays.

A 360° rotation with 10×12 cm. or 10×14 cm. centered at mid-pelvis is shown in Figure 5, A and C. The depth dose distribution was calculated by the simple computational method described by Gregory¹⁰ using the Braestrup and Jones methods. These calculations were checked by ionization measurements at certain points in an oval section 20×30 cm. plexiglas water phantom. There was a difference of ± 3 per cent, especially in the anteroposterior direction, and the whole distribution showed a flattening along this axis instead of the concentric circles ob-

tained by the computational method. From the clinical point of view we have used it with the hectocurie machines more for the sake of simplicity in the setting up of the patient than for a real physical advantage over the static field arrangement. In fact, in some patients the integral dose could be higher since laterally quite a thick slab of tissue is covered by the 40 to 50 per cent curve.

Bi-axial rotation therapy. Soon after Mellor¹⁹ in England published a technique of total pelvis irradiation by two separate lateral pendulations with a theratron, we started using this arrangement since it gives a good distribution for the whole pelvis with flattening in the anteroposterior direction and thus diminishing the dose to the bladder and rectum. Figure 5, B and D illustrates the technique using 160° lateral pendulation with 6×12 cm. field portals centered 2 cm. off the mid-line in the center of the parametrial region. A more homogeneous irradiation is obtained with a 9×12 cm. or 9×14 cm. field. This arrangement still irradiates the femur, but in certain units, like the theratron senior, the beam can be shut off while passing over this bone without any serious alteration of the depth dose distribution. This technique cannot be used with the 15 mev. betatron

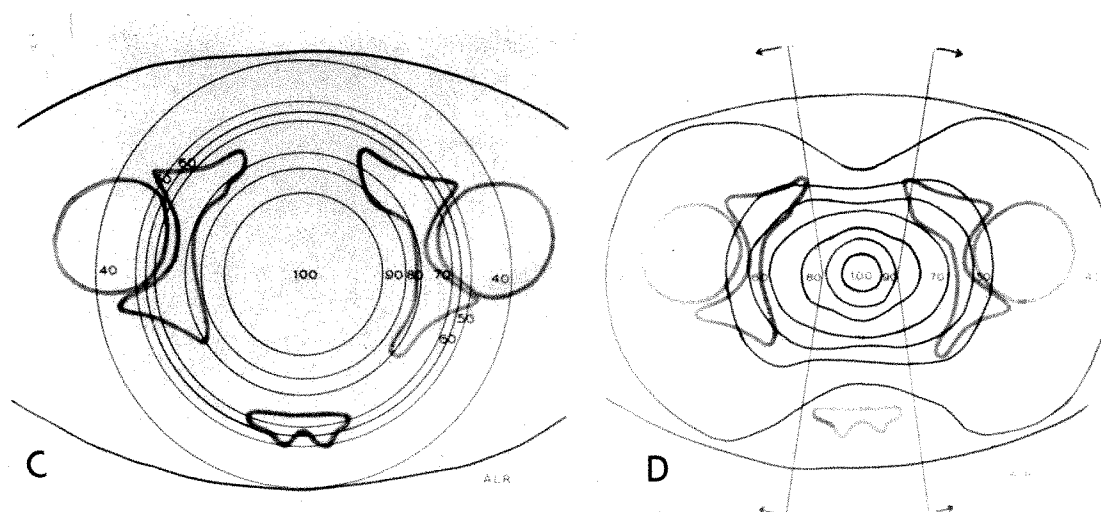


FIG. 5. Carcinoma of the cervix: Whole pelvis irradiation with moving field technique. (C) Depth dose distribution for *A* calculated by the simplified computational Gregory method. (D) Depth dose distribution for the technique shown in *B*. A better distribution is obtained using fields 9 cm. wide instead of 6 cm. This distribution cannot be reproduced with the 15 mev. betatron unit because of the lack of penumbra.

because either an undesirable superimposition of the beams is produced in the mid-pelvis or two separate volumes are obtained. This is due to the lack of penumbra which is responsible for the bow-tie sort of distribution obtained with the cobalt units. Within our short time practice using this technique, we are under the impression that a greater tolerance is gained.

Any of the above whole pelvis radiation treatments could be supplemented by

intracavitary radium at lower doses than those used with the parametrial techniques. They also can be supplemented by small volume concentration of an extra dose given by rotation therapy. This can be done, too, in extensive bladder carcinoma. After 5,500 to 6,000 rads are given to the whole pelvis, an extra 1,000 or 1,500 r can be delivered to a small volume in the primary tumor. This is illustrated in Figure 6, *A* and *B*, which shows three- and

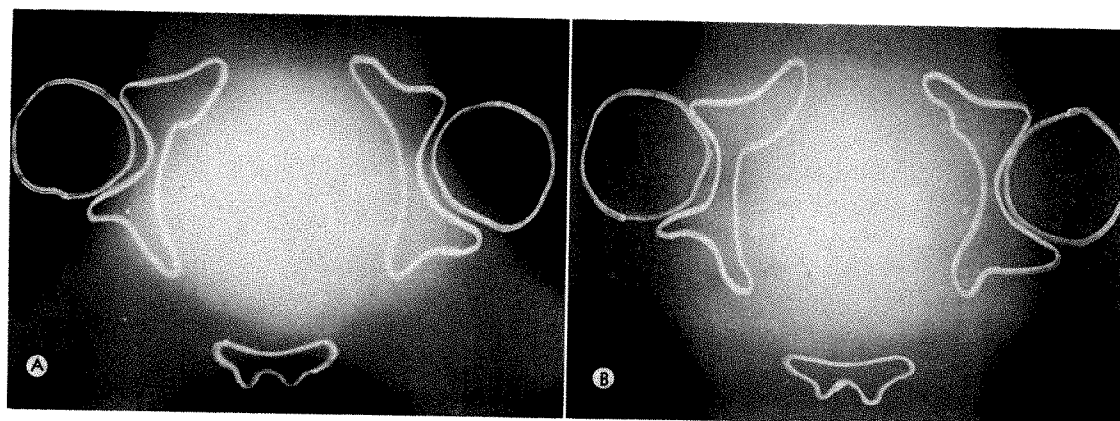


FIG. 6. Whole pelvis irradiation supplemented by small field rotation therapy. (A) Whole pelvis three-field technique (15×10 cm. anterior and two 10×10 cm. posterior) at 35° . Concentration with an 8×8 cm. field, 220° anterior pendulation. Bladder cancer treated with Co^{60} . (B) Whole pelvis four-field arrangement with a 6×6 cm. field at 360° rotation in mid-pelvis with Co^{60} . Useful for advanced carcinoma of the cervix.

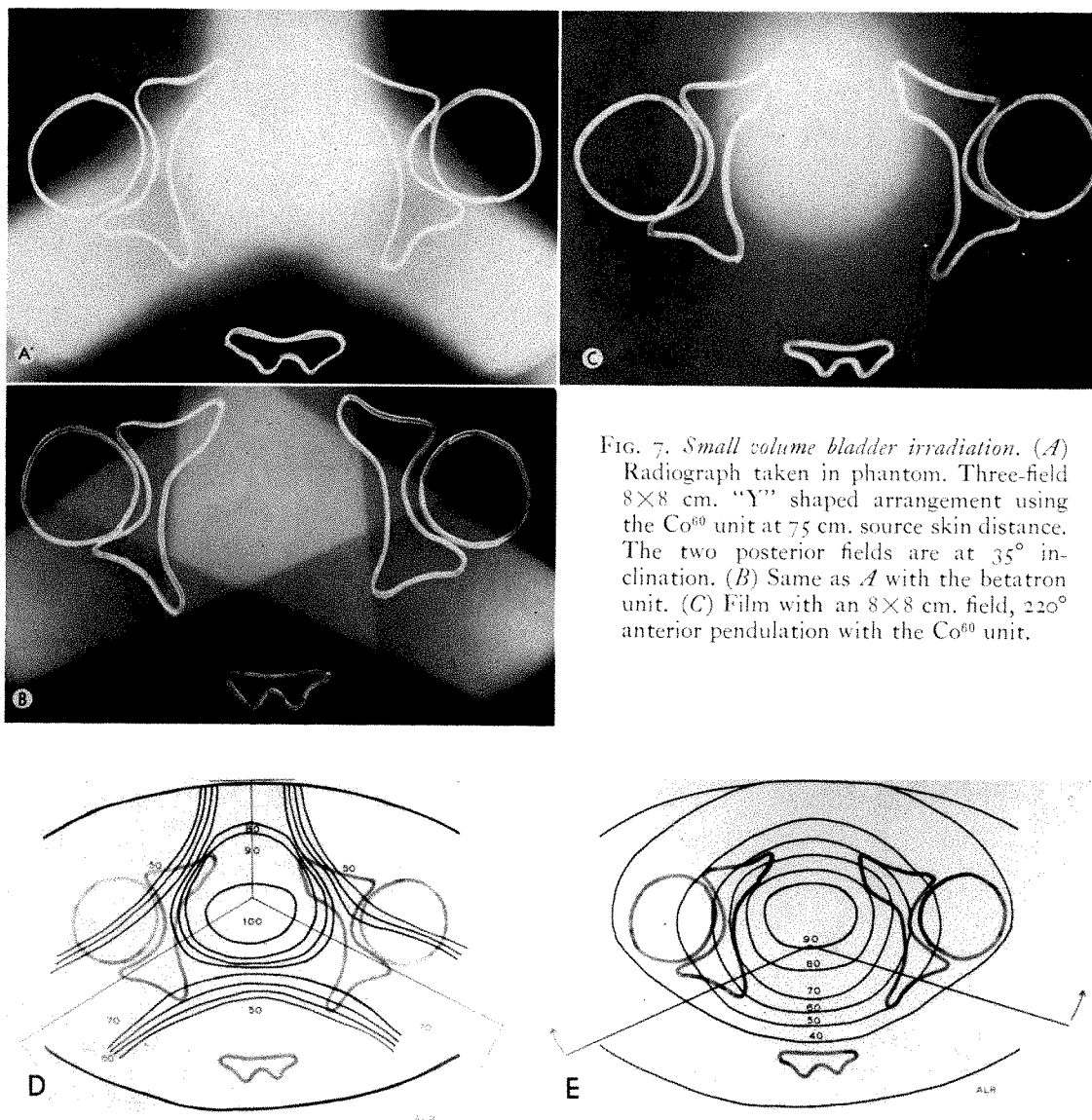


FIG. 7. *Small volume bladder irradiation.* (A) Radiograph taken in phantom. Three-field 8×8 cm. "Y" shaped arrangement using the Co^{60} unit at 75 cm. source skin distance. The two posterior fields are at 35° inclination. (B) Same as A with the betatron unit. (C) Film with an 8×8 cm. field, 220° anterior pendulation with the Co^{60} unit.

FIG. 7. *Small volume bladder irradiation.* (D) Depth dose distribution for A. (E) Depth dose distribution for C.

four-field arrangements supplemented by 220° anterior pendulation with an 8×8 cm. field for bladder or a box technique with an 8×8 cm. full rotation. This supplementary radiation can be more accurately limited and the benefit from a much higher depth dose can be obtained with the Siemens betatron. In carcinoma of the cervix, this supplementary radiation, either by radium or rotational external radiation, should be practically the rule since complete

sterilization of the primary lesion cannot, in the majority of cases, be achieved by whole pelvis external irradiation alone. It is obvious that to deliver 6,000 to 7,000 rads to the mid-pelvis by external irradiation is not the same as to give 20,000 r by radium.

CARCINOMA OF THE BLADDER

In our experience, carcinoma of the bladder treated with static fields at 250 kv. has produced disappointing results. Com-

plex cross firing techniques, requiring a very precise localization of the tumor to keep the fields as small as possible, made this type of treatment difficult and time consuming. The use of cone rotation improved this to some extent, but a more suitable and more constantly successful form of treatment was badly needed.

Improved results and better local and general tolerance have been reported with supervoltage therapy of this form of cancer. When the spread of the disease prevents limited interstitial treatment, external supervoltage irradiation seems to offer an adequate and useful method of treatment.

In moderately advanced, well differentiated tumors, a three-field technique with Co^{60} or better still with the betatron unit gives a high depth dose with good distribution in a limited volume as shown in Figure 7, *A*, *B* and *D*. In patients with partial cystectomy or in whom the bladder lies anteriorly, a 180° to 220° anterior pendulation is useful (Fig. 7, *C* and *E*).

In anaplastic or in very extensive infiltrating lesions, whole pelvis irradiation is indicated, using the larger portals with the three- or four-field arrangements described for whole pelvis irradiation supplemented by small field rotation therapy. A volume of 6×6 cm. to 8×8 cm. should receive an additional dose of 1,000 to 1,500 rads (Bloedorn³). Radiographs obtained when using this technique are shown in Figure 6, *A* and *B*.

The difference in the size and the position of the bladder in each patient requires an accurate localization of the tumor so as to be able to choose the best size and setting of the fields in each individual case. The localizing roentgenographic equipment attached to the 15 mev. Siemens betatron helps a great deal in this respect. For telecobalt units a localization radiograph should be taken for all portals with air or contrast material in the bladder.

SUMMARY

A comparison of several supervoltage radiotherapy techniques with static or ro-

tating fields was made for cobalt 60 and 15 mev. betatron units. For carcinoma of the cervix, parametrial techniques with two and three static fields were studied. With the 15 mev. betatron, an internal tangential rotation for parametrial irradiation is to be further studied. For advanced stages, whole pelvis irradiation by two opposing, three- and four-field arrangements for cobalt 60 and betatron units were studied and compared. Full rotation and bi-axial lateral pendulation for cobalt 60 were also studied.

The possibility of supplementary small volume rotational irradiation after whole pelvis irradiation is presented.

Three-field static and rotational techniques using the betatron and cobalt 60 units for bladder tumors are reviewed.

ACKNOWLEDGMENT

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The assistance of Ing. Lutz Vater was invaluable, especially in the work with the betatron unit. We would like to express our thanks to our Technicians: Miss Julia Hernández and Miss Elvira Pantoja for their assistance in photodensitometric measurements and to Ing. José Alvarez for the calibration of the telecobalt 60 units.

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ISODOSE CURVES AND RADIATION DISTRIBUTION ABOUT PATIENTS WITH INTRACAVITARY RADIUM SOURCES

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STIMULATED by the recent survey of Barry and Krueger² as well as by the scarcity of published detailed information on radium protection of patients with intracavitary radium or cobalt 60 sources, we decided to determine the radiation distribution around 10 such patients under treatment for malignant disease at the Tumor Institute of the Swedish Hospital. We used a Beckman Iometer model Mx4, which was calibrated against the National Bureau of Standards certified radium stocks.

The patients were positioned with the pubic region in the center of the bed. They were instructed to put their arms by their sides and to keep their legs together throughout the survey. The height of the upper surface of the bed mattress from the floor was 86 cm. Measurements of the gamma-ray exposure dose rate were taken with the geometric center of the ionization chamber in the positions shown on Figure 1. Readings were obtained 90 cm. from the floor except in the areas directly above the bed or above the patient. Positions VII and VIII were in the adjacent room nearest to the source. Position VII was close to the wall and Position VIII over the simulated position of the gonads of a patient in a bed against this wall.

Seven out of the 10 patients had an intravaginal or intrauterine insertion of 40 mg. of radium; 2 patients had 60 mg. of radium and 1 patient had 30 mg. of radium in an unshielded Bloedorn type vaginal applicator (Fig. 2-5).

In general, the isodose curves confirmed the results of previous investigations with the exception that the dose level at the foot of the bed was not found to be consistently higher than that at the head of the bed as

described by several authors.^{2,3,6,7} The increase of exposure dose noted in the midline at the foot of the bed is believed to be the result of decreased shielding by the patient's legs. The midline dose is further increased when the patient's legs are abducted. It is obvious that patients will not maintain a constant position in bed throughout the treatment so that the dose pattern will necessarily vary. Furthermore, in our cases the bed frame provided some shielding.

Measurements in the adjacent room behind a standard lath-and-plaster-wall (Positions VII and VIII, Table 1) are of critical importance. With sources of higher intensity (60-100 mg. of radium), a person next to the wall nearest to the source (Position VII) would be exposed to more than 2 mr/hr. Our readings, 1.10 m. from this wall (Position VIII), indicated that the exposure dose at this range did not exceed 2 mr/hr. for sources as intense as 100 mg. of radium. If the "restricted area" in the adjacent room can be avoided or if filtration is added to the portion of the wall close to the source, the patients, personnel, and visitors would be adequately protected.

The pelvic parameters of our patients, expressed by anteroposterior and lateral measurements at the pubic level and their weight, did not significantly influence the isodose pattern (Table 1). Other factors, such as the actual location of the source in the pelvis, are of more importance.

It has been suggested by Barry and Krueger² that a direct correlation exists between pubic dosimetry and all distal points. With Beckman Iometer and Victoreen chambers, we were unable to confirm this observation. Apparently, the distance between the radium and the abdominal wall

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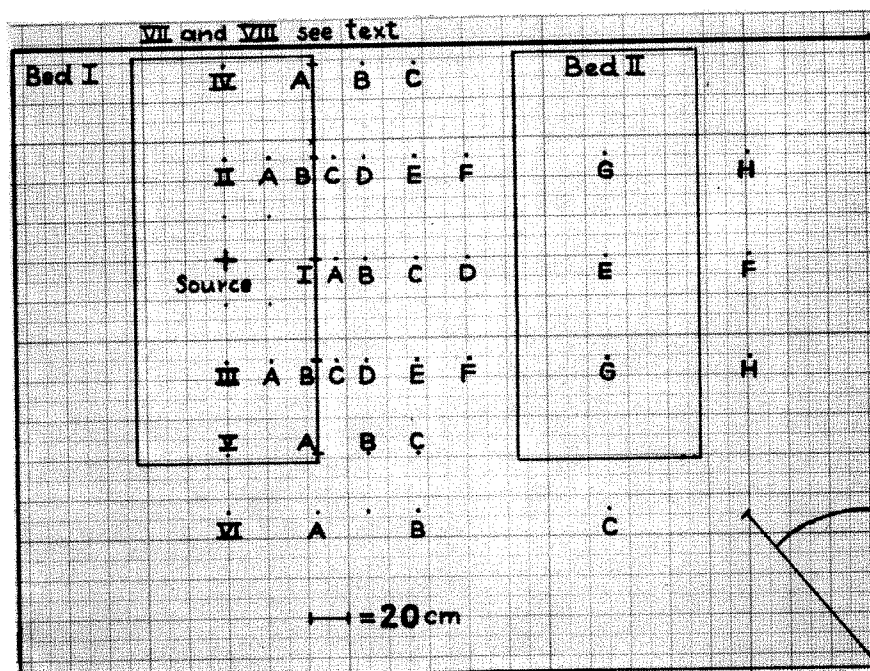


FIG. 1. Chart showing positions where measurements of gamma-ray exposure were taken.

varies considerably from patient to patient.

The recent changes in radiation protection regulations^{1,4,5} are such that every room with a patient containing an intracavitary radiation source as low in intensity as 10 mg. of radium, would be designated both a "restricted" and "radiation area" by Atomic Energy Commission standards. Personnel charged with the care of patients with intracavitary radium are likely to re-

ceive in excess of 25 per cent of the permissible dose for radiation workers, $1\frac{1}{4}$ rem/calendar quarter, and are thus required to use monitoring equipment. Different source intensities require varying limits upon the time spent close to the patient. These time limits can be precalculated by using Figure 1 and Table 1. Persons under 18 years of age should not be permitted to give nursing care to patients with intracavitary radium

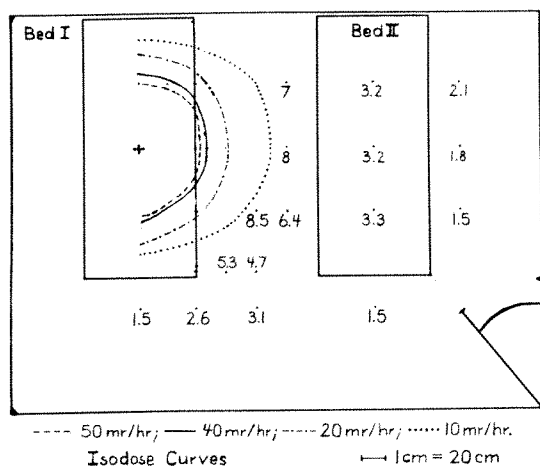


FIG. 2. Isodose curves with 30 mg. intracavitary radium source.

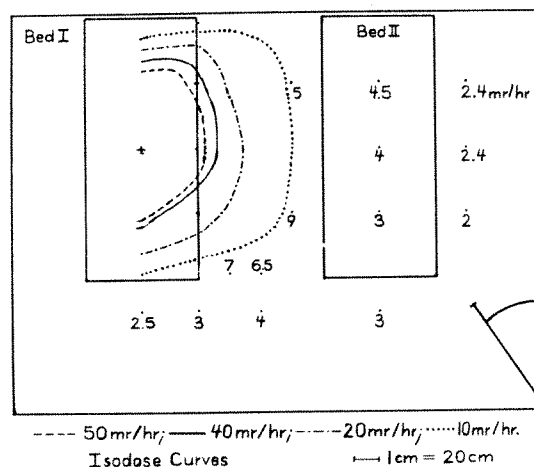


FIG. 3. Isodose curves with 40 mg. intracavitary radium source.

TABLE I
READINGS AND THEIR AVERAGES IN STANDARD POSITIONS (SEE FIG. 1) CORRECTED TO A 10 MG. RADIUM SOURCE

Radium Source	Pelvis		Weight (lb.)	+	I	IA	IB	IC	ID	IE	IF	II	IIA	IIB	IIC	IID	IIE	IIF	IIG	IIH	III	IIIA
	AP	LAT																				
30 mg.	20	33	136	266	19.3	13.3	7.0	4.0	2.7	1.1	0.6	16.7	16.3	9.0	6.3	5.7	3.3	2.3	1.1	0.7	18.3	9.7
40 mg.	18	31	120	250	18.0	11.3	6.5	2.8	2.5	1.0	0.6	15.5	15.8	11.0	6.8	4.5	3.8	2.4	1.1	0.6	14.3	8.8
40 mg.	17	30	115	263	25.0	14.8	8.5	4.3	3.1	1.4	0.9	12.3	15.5	11.0	7.8	6.0	4.8	2.8	1.2	0.8	37.5	20.0
40 mg.	17	30	135	175	20.0	11.8	7.3	4.5	3.0	1.8	—	14.5	15.8	10.3	6.5	4.5	3.0	2.5	1.5	—	9.0	6.3
40 mg.	16	31	125	453	22.0	15.0	8.8	5.0	3.3	1.2	0.5	37.8	29.5	15.5	10.5	7.0	5.3	3.5	1.3	—	15.0	5.8
40 mg.	18	31	136	300	20.0	13.0	7.5	5.0	3.0	1.1	0.4	13.8	12.5	9.5	7.5	5.0	3.5	2.5	1.1	0.5	19.3	8.3
40 mg.	17	28	135	213	20.0	11.5	7.5	4.3	3.0	—	—	25.0	17.5	11.3	8.3	6.3	4.3	3.3	—	—	8.8	4.8
40 mg.	17	29	123	262	17.0	11.5	7.7	4.0	2.8	1.1	0.2	24.2	20.0	13.0	11.8	6.5	4.8	3.0	1.1	0.2	10.3	4.8
60 mg.	21	33	139	333	22.5	13.3	8.3	4.7	3.2	2.3	0.8	27.5	23.3	14.1	8.0	6.1	4.0	2.8	2.3	0.8	14.0	8.0
60 mg.	18	29	118	333	24.2	15.0	8.0	4.7	3.2	1.0	0.6	11.8	13.3	8.2	6.0	5.0	3.7	2.7	1.2	0.6	14.0	7.3
Average mr./hr./10 mg. Ra					20.8	13.1	7.7	4.3	3.0	1.3	0.6	19.9	18.0	11.3	8.0	5.7	4.1	2.8	1.3	0.6	17.4	8.8
Radium Source	IIIB		IIIC	IIID	IIIE	IIIF	IIIG	IIHH	IIIV	IIIVA	IIIVB	IIIVC	V	VA	VB	VC	VI	VIA	VIB	VIC	VII	VIII
30 mg.	7.3		5.7	4.0	2.8	2.1	1.1	0.5	1.0	1.7	1.4	1.0	1.3	1.7	1.8	1.6	0.5	0.9	1.0	0.5	0.8	0.2
40 mg.	7.8		6.3	4.4	4.3	2.3	0.8	0.5	1.9	2.1	2.3	2.0	2.5	1.9	1.8	1.6	0.6	0.8	1.0	0.8	0.5	0.2
40 mg.	14.3		8.8	5.8	4.0	2.8	1.2	0.8	1.3	1.8	2.4	2.6	1.3	2.5	2.4	2.0	0.8	1.1	1.3	0.8	—	—
40 mg.	9.0		6.3	5.0	3.3	2.1	1.5	0.9	2.0	2.3	2.8	2.3	2.8	2.1	2.0	1.8	1.1	1.1	1.1	0.9	—	—
40 mg.	5.8		3.7	3.8	2.3	2.3	1.1	0.4	5.5	3.3	2.3	2.1	1.3	0.8	0.9	0.9	0.7	0.5	0.6	0.5	0.5	0.1
40 mg.	7.5		5.5	4.8	2.8	2.3	1.1	0.5	3.0	3.0	2.5	2.3	2.8	1.8	1.5	1.4	0.8	0.6	1.0	0.5	0.4	0.3
40 mg.	4.8		4.3	4.0	2.5	2.3	—	—	6.0	3.5	3.0	2.5	2.5	1.1	1.3	1.3	1.5	0.8	1.0	—	0.5	0.1
40 mg.	4.0		3.8	3.0	2.3	1.8	0.8	0.2	4.3	4.0	2.5	2.0	2.0	1.8	1.3	1.1	0.8	0.9	0.8	0.5	0.4	0.2
60 mg.	6.8		5.8	4.1	3.3	2.5	1.1	0.8	2.5	2.0	2.0	2.5	2.8	1.3	1.4	1.5	1.5	0.7	0.8	0.8	—	—
60 mg.	7.0		6.3	4.5	3.3	2.5	0.9	0.5	2.7	3.0	2.5	2.0	3.2	1.3	1.7	1.5	0.5	0.6	0.9	0.6	0.4	0.3
Averages /10 mg.	7.4		5.7	4.3	3.2	2.3	1.1	0.6	3.0	2.7	2.4	2.1	2.3	1.6	1.6	1.5	0.9	0.8	1.0	0.7	0.5	0.2

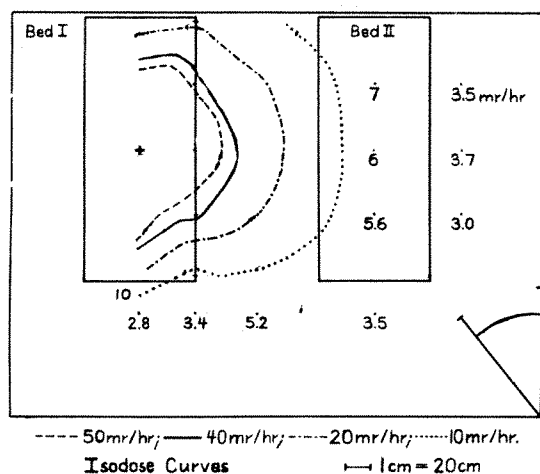


FIG. 4. Isodose curves with 60 mg. intracavitary radium source.

nor allowed in the room as visitors. Other visitors should be instructed to stay in relatively safe areas and the time limit should be specified so that a maximum permissible dose of 10 mrem/week is not exceeded.

It is obvious that a patient in the bed next to one receiving radium treatment would be exposed to a dose well in excess of the permissible dose. It appears that one would be justified in allowing patients in the next bed who are also receiving some form of major radiotherapy over their gonads. However, the additive effect of two radium sources in patients close to each other (Fig. 5) would further complicate the radiation protection of personnel engaged in the nursing care.

For reference purposes, all readings in Table I are adjusted to the locations shown on Figure 1 and corrected to a 10 mg. radium source. The averages of these values (Table I) provide an index for the calculation of the radiation distribution around sources of variable strength. After multiplication by the appropriate factor to obtain the source intensity under consideration, these averages in mr/hr. may be determined.

SUMMARY

The radiation distribution around 10 patients with intracavitary radium sources of

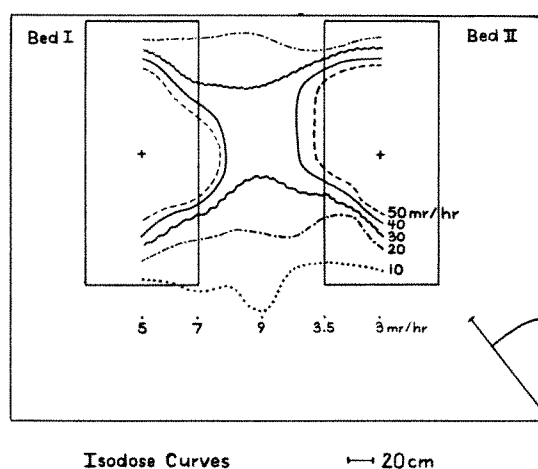


FIG. 5. Isodose curves with two 40 mg. intracavitary radium sources in proximity to one another.

different intensities was determined by means of a calibrated Beckman Iometer. The averages of the readings in standard positions corrected to a 10 mg. radium source provide an index for the calculation of this radiation distribution.

Radiation protection problems are discussed in the light of the results and the new standards recommended by the Atomic Energy Commission.

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RADIOTHERAPY OF EWING'S SARCOMA

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A REPORT of 165 cases of Ewing's sarcoma seen at the Mayo Clinic from 1905 through 1959 has been published recently.² The interested reader is referred to this review for the pertinent pathologic, clinical and surgical details of our experience with this primary malignant tumor of bone. This group of 165 patients included 120 in whom radiotherapy played a definitive role in the primary treatment, and it is with this group and its radiotherapy that this paper is primarily concerned.

These 165 patients, comprising somewhat less than 10 per cent of the total with primary malignant bone tumors in the Mayo Clinic series, ranged in age from an eighteen month old girl with a femoral tumor to a fifty-nine year old man with primary involvement of a rib. However, almost 90 per cent of them were less than thirty years of age and, as usual for Ewing's sarcoma, males predominated in a ratio of 101:64.

The pelvic girdle and the long tubular bones of the extremities accounted for about three quarters of these Ewing tumors. Although it is often stated that Ewing's sarcoma characteristically affects the diaphysis of the long tubular bones, the metaphysial regions of these bones were more commonly the epicenter of the growth in this series. The relative immunity of the distal portions of the extremities is emphasized by the absence of Ewing's sarcoma in the hands in this series, although the tumors in 4 cases did occur in the feet.

GROUPING OF PATIENTS BY TREATMENT

Of the 120 patients for whom radiotherapy was employed at some stage in the treatment, 55 were treated exclusively by

the intensive erythema-dose technique, which was discontinued at this institution around 1950. This method was employed in the overwhelming majority of Ewing's sarcomas treated radiotherapeutically up to that time. During the past decade, however, it has given way to the more conventional high-dose fractional techniques, the majority of which have been given with cobalt teletherapy. Of these 55 patients treated with the erythema-dose method, 16 received only a single series of treatment for one reason or another. This is considered to be inadequate therapy, and thus these 16 patients are placed in an incomplete erythema-dose category. The remaining 39 patients received the recommended two or more series and are placed in a complete erythema-dose group.

Another 16 patients, all but 2 of whom were seen since 1950, were treated exclusively with what by present standards might be called adequate fractionated therapy, namely a tumor dose of more than 3,500 r; in fact, all but one of these 16 patients received more than 4,000 r. An additional 34 patients received primarily surgical management, namely local excision, amputation or disarticulation, that was supplemented with preoperative or postoperative radiotherapy. The remaining 15 of the total group of 120 patients had recognized distant dissemination of the malignant process when first seen at the clinic; consequently, they are placed in a palliative radiotherapy group.

ERYTHEMA-DOSE RADIOTHERAPY

The short-term, intensive therapy called the "erythema-dose technique" employed prior to 1950 consisted of the administration in single doses of 500 to 600 r (air),

* The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

considered to be erythema-producing doses with the quality of radiation then employed, to three or four fields circumferentially about the part involved. With deep-seated lesions in the trunk or when the anatomic characteristics of the part precluded a multiple-port, cross fire technique, a simple two-field, opposing-port method occasionally was employed. Generally speaking, the initial series in such therapy afforded a tumor dose varying from 800 to 1,400 r in two to eight days, depending on the thickness of the part and the number of portals employed.

As already indicated, this single series of treatments never was considered as a complete course, and it was considered essential to recommend a second such series one or two months after completion of the initial series if possible, providing that general dissemination of the tumor or

rapid decline in the patient's general health did not militate against further radiotherapy. A third series and possibly additional series often were recommended in three to six months, depending on the response of the tumor.

The importance of the repetition of this therapy is illustrated in the difference in results between patients receiving only the initial series of the erythema-dose treatment and those receiving two or more such series (Table 1). All 16 patients receiving only the initial series were dead in less than two years; of the 39 patients receiving two or more such series, 6 (15 per cent) lived for two to five years and an additional 6 lived more than five years.

The question that immediately arises is whether the better results obtained in the patients receiving complete erythema doses were produced by any intrinsic merit in

TABLE I
RESULTS OF RADIOTHERAPY IN EWING'S SARCOMA

Type of Treatment	Cases	Survivors					
		>Five Years		Two-Five Years		<Two Years*	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
Incomplete erythema-dose technique	16	0	0	0	0	16	100
Complete erythema-dose technique	39	6	15	6	15	27	70
Total	55	6	11	6	11	43	78
Conventional fractionated radiotherapy (>4,000 r tumor dose)							
Roentgen therapy	6	1	17	2	33	3	50
Cobalt teletherapy	10	0	0	2	20	8	80
Total	16	1	6	4	25	11	69
Surgery+preoperative irradiation	6	3	50	1	17	2	33
Surgery+postoperative irradiation	15	1	7	1	7	13	86
Total	21†	4	19	2	10	15	71
Palliative radiotherapy for metastasis	15	0	0	1	7	14	93

* Includes recently treated patients with metastasis.

† Exclusive of 13 cases in this category in which radiotherapy probably was superfluous.

the actual repetitiveness of the treatment and the higher total doses obtained thereby or whether the process of natural selection was a factor. Those patients with more advanced disease or those destined to succumb early to their disease might be eliminated from the competition early, so to speak, leaving the bulk of the more favorably disposed patients as the only ones in which repeat therapy is possible or advisable. This factor must enter into evaluation of the merits of the erythema-dose technique, but its relative importance can be minimized when one considers that of the 15 patients receiving only the initial series, excluding one lost to follow-up, only one (7 per cent) died within three months after the onset of therapy, whereas 2 (5 per cent) of the 39 patients receiving two or more such series died within three months. In every case in which a second series of treatments was given, the repeat therapy was begun within two or three months from completion of the initial series. Thus, early death when conditions are less favorable and the subsequent process of selection do not appear to be prime factors in explaining the better results obtained in patients receiving two or more series of treatments with the erythema-dose technique.

FRACTIONATED RADIOTHERAPY

As already mentioned, 16 patients were treated entirely by radiotherapeutic means, excluding, of course, surgical biopsy; this group received, by present standards, adequate fractionated radiotherapy. All but one of these 16 patients received a tumor dose in excess of 4,000 r, a level that I consider optimal for orthovoltage therapy in Ewing's sarcoma. Disappointingly and completely contrary to expectations, the salvage rate obtained in this favorable "high dose" group was worse than that seen with the older and discarded erythema-dose technique (Table I). Of the 16 patients receiving high-dose therapy, 10 of whom had radiocobalt therapy in doses ranging from 4,000 to 6,200 r, only one (6 per cent)

lived more than five years and 4 (25 per cent) lived from two to five years.

Five patients in this group were of uncertain status; 2 were lost to follow-up but had metastatic implants when last heard from and are presumed dead of their disease; the other 3 were treated recently but all had known metastasis when last heard from and presumably will shortly be dead of their disease. With known metastatic growths present in all 5, it is assumed that they will be ineligible for five-year survival statistics, because not a single one of these 120 patients survived for five years after onset of therapy if dissemination of the sarcoma subsequently became manifest.

PRIMARY SURGERY PLUS RADIOTHERAPY

The best results in the series were obtained in the 34 patients in whom primarily surgical treatment was reinforced with preoperative or postoperative radiotherapy. However, this group contains 13 patients in whom the irradiation probably was superfluous and could not have contributed much one way or the other to the success or failure of treatment. These were patients in whom so-called "prophylactic irradiation," long since discontinued at the clinic, was given to the stump of an extremity after amputation, to regional axillary or inguinal lymph nodes, or occasionally even to the mediastinum or lung fields or both.

In the remaining 21 patients in this group of 34, irradiation might be said to have played a part in the control or lack of control of the local disease (Table I). This treatment usually consisted of either preoperative irradiation, in some cases given years before operation eventually became necessary for uncontrolled disease, or postoperative radiotherapy usually given to the tumor bed immediately after surgical excision of a Ewing sarcoma somewhere on the torso, such as the clavicle, ribs or scapula.

Preoperative Radiotherapy. Preoperative irradiation appears to have been the more successful. Six of the 21 patients received

preoperative therapy, and 3 of these have survived five years or more. One of these survivors (Case I) is of particular interest in that the case demonstrates well the occasional great radiosensitivity of Ewing's sarcoma.

CASE I. An eleven year old girl with an osseous neoplasm of the lower third of the left radius underwent biopsy elsewhere, with a diagnosis of Ewing's sarcoma being established. Radiation therapy to the entire left arm was started, being interrupted after two days when the child was brought to the clinic. The radiotherapy at home was as follows: the first day, 200 r (air) was given to each of three anterior fields, one covering the forearm, another the arm and a third the axilla and supraclavicular space; on the next day, correspondingly opposed posterior fields were each given 250 r, all with 200 kv. and a half-value layer of 0.9 mm. of copper. In all probability, a tumor dose of 550 r was not exceeded.

At the clinic, local excision of the involved portion of the radius was done, with a bone graft applied to bridge the defect produced. Microscopic study of the excised portion of bone revealed extremely few, almost unrecognizable tumor cells remaining. This patient has remained alive and well without evidence of disease for fifteen years after operation.

In addition to the 3 five-year survivors, another of these 6 patients lived for more than two years. With the small numbers involved, these results cannot be statistically significant, but they do represent an outcome appreciably better than that obtained with more conventional methods.

Postoperative Radiotherapy. The other 15 patients in this group of 21 received postoperative radiotherapy, usually after local excision of a Ewing sarcoma affecting some part of the torso. Irradiation followed local excision in 3 cases of neoplasms involving the clavicle, in 6 involving one or more ribs and in 5 involving the scapula; the remaining patient received irradiation after local excision of an involved fibula.

The results of combined therapy in these patients were not so good as those with preoperative treatment. Only one patient survived for more than five years, and one

other survived for more than two years before succumbing to his disease. However, these two groups of patients are not at all comparable. Of the 6 patients receiving preoperative radiotherapy, 5 had neoplasms involving an extremity, in which the salvage rate is expectedly higher; this included all 4 of those surviving for more than two years. Of the 15 patients receiving postoperative radiotherapy, 14 (93 per cent) had neoplasms of the trunk (ribs, clavicle or scapula), in which the salvage rate is understandably much lower.

PALLIATIVE RADIOTHERAPY

A group of 15 patients with early spread of the disease recognized at the time of their first definitive treatment here subsequently were placed in the palliative group. Eight of these patients had obvious dissemination to the lungs when they were first referred for palliative radiotherapy to the primary lesion. Seven of the 15 patients had recognizable spread to other portions of the skeletal system (one of these had additional intra-abdominal spread) and one patient had only intra-abdominal involvement.

As might be expected, none of this group survived for five years. Only one patient was living at last report; this patient was alive two and one-half years after her initial therapy, but she had widely disseminated metastatic tumors throughout the lungs, skeletal system and peripheral lymph nodes.

The following case demonstrates the value of palliative radiotherapy in the face of an otherwise hopeless prognosis.

CASE II. After prior biopsy elsewhere showed Ewing's sarcoma of the right femur (neck and intertrochanteric portion), an eighteen year old boy was referred to the clinic for definitive therapy. Between September 14 and October 14, 1953, a tumor dose of 5,250 r was administered to the upper half of the femoral shaft and head, and a tumor dose of 3,050 r was delivered to the lower half of the right femoral shaft. The technical factors employed were 250 kv., a treatment distance of 50 cm. and a half-value layer of 1.3 mm. of copper.

Subsequent examinations in January and August, 1954, and June, 1955, revealed roentgenologic evidence of good resolution of the bony neoplasm and no evidence of distant dissemination. In December, 1955, although the patient was still asymptomatic, roentgenograms disclosed renewed activity of the femoral neoplasm. Hindquarter amputation was advocated; after this was refused by the patient, additional radiation therapy was given. However, because of extensive roentgen tanning and atrophy from previous treatment, only a limited amount of radiation was thought advisable; between December 27 and December 30, 1955, an additional tumor dose of 1,000 r was administered, employing cobalt teletherapy at an 80 cm. skin-to-source distance.

In September, 1957, there was evidence of further progress and reactivation of the neoplasm, a pathologic fracture through the main component of the tumor, and extension of the neoplasm both proximally into the femoral head and distally into the femoral shaft; therefore, an interinnomino-abdominal (hindquarter) amputation was done.

In November, 1957, thoracic roentgenograms revealed a 3 cm. nodular metastatic tumor in the left midlung field and probably bilateral hilar lymph node metastasis. Between January 6 and January 25, 1958, a midplane tumor dose of 2,300 r was administered to the entirety of both lung fields. The technical factors employed were 250 kv., a 70 cm. treatment distance and a half-value layer of 1.8 mm. of copper; opposing anterior and posterior 24 by 26 cm. fields were treated on alternate days.

The patient was next examined eighteen months later, in July, 1959. In the interim, he had been entirely well, gaining in weight from a previous 110 pounds (50 kg.) to a robust and healthy 220 lbs. (100 kg.). Thoracic roentgenograms revealed complete resolution of the parenchymal and hilar metastatic growths previously noted. When last heard from in June, 1960, two and one-half years after treatment of the pulmonary deposits, the patient was still in excellent health. Thoracic roentgenograms remained completely free of any evidence of disease.

COMMENT

The failure to show substantial improvement over previous five and ten year survival rates in Ewing's sarcoma with more aggressive local irradiation, while a dis-

appointment, is not entirely unexpected. Recent literature has not indicated any significant betterment of the conventional 10 to 15 per cent five year survival rates with either more radical surgical intervention or more aggressive local radiotherapeutic measures. The ultimate in total eradicability of this osseous malignant tumor, namely surgical amputation or disarticulation well proximal to the neoplasm, has not yielded more than a 15 per cent five year salvage, and it is not to be expected that local radiotherapy, regardless of how aggressively it is given or how desirable the limb-saving potential of radiotherapy may be, can better this yield.

Almost without exception, the 85 to 90 per cent failure rate of therapy in Ewing's sarcoma results not from failure to control the local disease but from systemic dissemination either before or at the time of the first definitive therapeutic endeavors. While heretofore treatment has been directed almost exclusively at the primary neoplasm, it is becoming more and more apparent that Ewing's sarcoma is in most cases a systemic disease and that, if any significant improvement in salvage rates is forthcoming, therapy will have to be directed toward the systemic component or metastatic element, as well as the primary neoplasm.

After the initial report of Cole and associates¹ regarding the presence of malignant cells in fluid perfused through the artery and collected from the vein of a cancerous segment of colon removed surgically, other authors in increasing numbers have been reporting the finding of circulating malignant cells in the blood stream of patients with malignant neoplasms. Engell,³ in 1955, found tumor cells during operation in the peripheral blood in 10 of 79 patients (13 per cent) with various types of malignant tumors and in 7 of 14 patients (50 per cent) who had inoperable malignant growths. Fisher and Turnbull,⁵ in 1955, found tumor cells in the blood obtained from mesenteric veins in 8 of 25 specimens (32 per cent) of colorectal carcinoma. Moore and co-workers^{7,8} reported car-

cinoma cells in the peripheral blood in 93 of 179 patients (52 per cent) with carcinoma and in the blood draining tumor sites in 60 of 109 such patients (55 per cent). Other observers^{6,9,10} have reported finding significant numbers of patients with malignant cells in the blood stream in various types of malignant neoplasms, and there appears to be little doubt that the incidence of embolization of tumor cells is appreciably higher than has been suspected heretofore.

Of particular interest in relationship to Ewing's sarcoma was Engell's⁴ finding that the venous spread of carcinoma cells during resection of a tumor depends primarily on the histologic grade of the tumor and to a lesser degree on the local extension of the primary neoplasm. In a study of 125 patients, most of whom had intestinal carcinoma, malignant cells were found in the blood of 76 patients; these cells were noted in the blood stream of 34 per cent of the patients with Grade 2 tumors, 76 per cent of those with Grade 3 tumors and 100 per cent of those with Grade 4 tumors. These figures would correlate well with Ewing's sarcoma, always a Grade 4 neoplasm, with its attendant 85 to 90 per cent lethality.

However, it would be a mistake to conclude that the demonstration of malignant cells in the peripheral blood is tantamount to a death sentence. Of Engell's⁴ aforementioned 125 patients, 55 were alive after five to nine years, and 28 of these had malignant cells in the blood at the time of operation. Moore and associates^{7,8} stated that probably 99.9 per cent of all malignant cells released into the blood stream fail to survive and establish metastatic deposits. Other factors obviously are operative in determining whether these circulating malignant cells will "take," and the implication is that measures are urgently needed to reinforce the natural defense mechanisms of the body or at least allow them to function at peak capacity.

Efforts are now under way at this institution to augment the effectiveness of conventional measures, such as radical surgical treatment and intensive local irradiation of

the primary neoplasm. These supplemental measures include the use of radio-phosphorus both before and after operation and before the institution of radical irradiation, and the use of chemotherapeutic agents such as nitrogen mustard administered both systemically and by means of perfusion directly into the affected limb. Efforts are also under way to achieve better delineation of the role of preoperative radiotherapy as an integral part of the planned surgical approach to this disease; these have been under investigation somewhat longer than have the newer adjuvant measures just mentioned. However, Ewing's sarcoma is a relatively rare tumor, and a sufficient number of patients have not been treated with these supplemental measures nor has enough time elapsed at this writing to allow any idea of the value of these procedures.

CONCLUSIONS

More aggressive radiotherapy has failed to produce material improvement in the salvage rates in Ewing's sarcoma. This, along with a similar failure of earlier and more radical surgical intervention to improve the salvage rates, probably is indicative of factors in the control of this disease beyond the influence of the best efforts of the surgeon and the radiotherapist acting either singly or in combination. A heretofore unsuspected high incidence of embolization of malignant cells into the peripheral blood stream, especially in association with the more undifferentiated malignant neoplasms, is under general indictment and investigation. It is toward this metastatic or systemic component of Ewing's sarcoma that attention is currently being directed, and efforts are being made with both chemotherapeutic and radioisotopic agents to augment the salvage rate obtained with local radiotherapy or radical operations.

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CLINICAL USE OF SHORT SOURCE-SKIN DISTANCE CESIUM 137 TELETHERAPY UNIT*

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THE original teleradium units, designed in the early 1920's, offered skin sparing and rapid fall-off of depth dose. This combination of beam characteristics has advantages for special clinical situations. The advent of other types of high energy irradiation and the drive to increase depth doses limited the development and application of teleradium units in the 1930-1940 decade. However, in England and Sweden, elaborate teleradium units were designed and later remodeled to accommodate cobalt 60 sources to provide higher dose rates while retaining a short source-skin distance (SSD).^{8,9,13}

Short SSD units with cesium 137 offer advantages similar to those of the earlier teleradium units.¹ There is rapid decrease of dose with depth and clinically useful skin sparing. Compared with cobalt 60, the lower energy of cesium 137 gamma emission permits the design of a more compact unit to provide the same degree of protection. Less room shielding is required, and beam-shaping devices can be made conveniently smaller. The reduced head size enables the use of shorter SSD's and facilitates treatment positioning. The tissue absorption is only slightly greater, while the longer half life is economically advantageous.

APPARATUS

A short SSD cesium 137 unit (Fig. 1A) described previously⁴ was installed in March, 1959. Containing approximately 800 curies of cesium 137, the source is 2.86

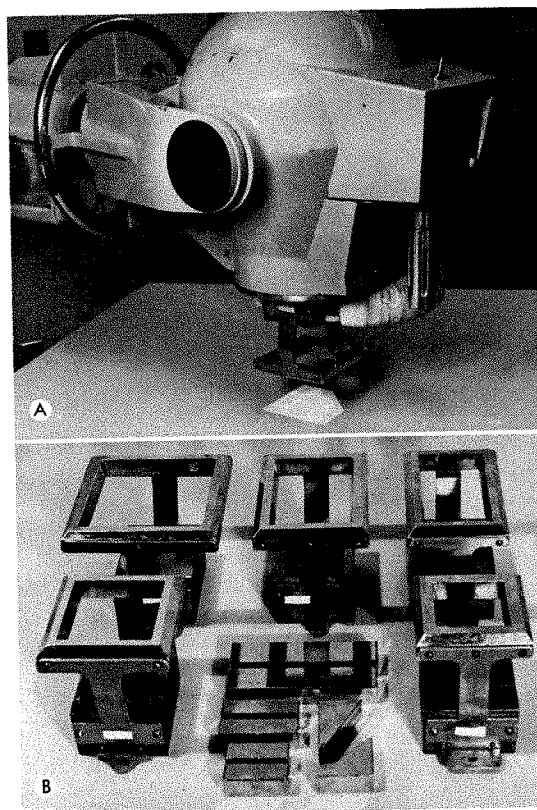


FIG. 1. (A) Short SSD cesium 137 teletherapy unit. The collimation has been modified to permit the use of interchangeable cones which incorporate a fixed secondary diaphragm to block penumbra. A light localizer defines field edges. Irregular fields are achieved by additional secondary beam shaping blocks. An electromagnet removes the secondary electrons emitted from the inside surface of the cone. (B) Treatment cones and secondary blocks. An assortment of these provides a wide range of flexibility. Maximum field size is 16 by 16 cm. at 30 cm. SSD. Secondary blocks are nickel plated to reduce electron emission.

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cm. in diameter and delivers 217 rhm, or approximately 77 rads per minute at a treatment distance of 22 cm. The unit was provided with a multiple-leaf adjustable diaphragm and light localizer. The minimum practical SSD for clinical use was 22 cm. with a maximum field size, at that distance, of 10 by 10 cm. as defined by the 55 per cent isodose level.

A need for larger effective field sizes and the desirability of sharper field edges led to the design of a series of interchangeable cones (Fig. 1B) to replace the adjustable diaphragm. An assortment of "open" cones allows maximum field size while blocking the penumbra. A minimum SSD of 20 cm. is practical with a maximum field size of 12 by 12 cm. as defined by the 80 per cent isodose level. Varying the SSD from 20 to 30 cm. provides wide flexibility and a maximum field size of 16 by 16 cm. at 30 cm. SSD. The light localizer allows direct visualization of the field through the "open cone." Additional secondary blocks may be superimposed for further beam shaping.

DOSIMETRIC CONSIDERATIONS

1. OUTPUT

The exposure dose rate, or "air dose," is conveniently expressed as roentgens per minute and is measured by a Victoreen chamber with a lucite cap to provide full build-up. The output varies with SSD in close approximation to the inverse square law. The output varies by less than 1 per cent with the interchangeable cones, for changes in field size from 6 by 6 cm. to 12 by 12 cm.

2. GIVEN DOSE

Treatment times are determined for the dose, in a tissue-equivalent phantom, at the depth of maximum electron build-up. It is called "given dose." It is the output in air plus the contribution of scatter and is commonly expressed in rads (energy absorbed in muscle). The conversion method is outlined in the *National Bureau of Standards Handbook*, No. 62 (1957). The con-

tribution of scatter with varying field sizes ranges from 0 to 7 per cent.

3. SHIELDING

The half-value layer (HVL) of the primary beam was found to range from 6 to 7 mm. of lead, corresponding to 11 to 14 mm. of copper and 4 to 5 mm. of tungsten. Compared with cobalt 60, the same effective shielding is achieved by much less absorber material. Collimators and beam-shaping devices can be made proportionately smaller, lighter, and simpler, to allow more versatility and closer approximation of the source to the patient.

4. BONE ABSORPTION

The ratio of absorption of energy in bone compared with soft tissue is 1.8 for 1.5 mm. Cu HVL, 1.06 for cesium 137 and 1.04 for cobalt 60.^{11,18} The difference between calculated and measured dose when bone is traversed may reach 10 to 20 per cent for 1.5 mm. Cu HVL, whereas with cobalt 60 or cesium 137, it seldom exceeds 2 to 3 per cent.

5. CENTRAL AXIS DEPTH DOSE

With short SSD units, the rapid fall-off of dose along any ray is predominantly a function of the inverse square law, tissue absorption playing a secondary role. Central axis depth doses for usual field sizes are given in Table I. Comparative depth doses for various energies and SSD's are given in Table II.

6. DOSE DISTRIBUTION

With short SSD the beam encompasses a greater area at a depth than it does on the surface (Fig. 2). Because of the large source size, the penumbra is more prominent. Flatness of the curves is more difficult to achieve, but with interchangeable cones and secondary blocks close to the skin the isodose curves are effectively flat with satisfactory sharpness of beam edges (Fig. 3).

With adjacent fields, high dose areas develop at a depth because of the beam divergence and penumbra (Fig. 4A).

TABLE I
CESIUM 137
PERCENTAGE DEPTH DOSES
(20.5 cm. Source-Skin Distance)

Depth (cm.)	Field Size (cm. ²)					
	16 (4×4)	25 (5×5)	36 (6×6)	64 (8×8)	100 (10×10)	144 (12×12)
0.13	100	100	100	100	100	100
1.0	90.0	91.0	91.5	92.0	92.0	92.0
2.0	79.0	80.5	81.0	81.5	81.5	81.5
3.0	68.5	70.0	71.5	72.5	73.0	73.5
4.0	59.5	61.5	62.5	63.5	64.8	65.0
5.0	52.0	53.5	54.5	56.5	57.0	57.5
6.0	45.0	46.5	48.0	50.0	51.0	51.5
7.0	39.0	40.5	42.0	44.0	45.1	45.5
8.0	34.0	36.0	37.5	39.0	40.2	40.6
9.0	29.7	31.5	33.0	34.7	35.6	36.0
10.0	26.2	27.5	29.0	30.8	31.8	32.3
11.0	22.7	24.0	25.6	27.4	28.2	29.0
12.0	20.0	21.5	22.7	24.5	25.3	25.8
13.0	17.5	19.0	20.0	21.7	22.6	23.0
14.0	15.3	17.0	18.0	19.4	20.3	20.7
15.0	13.5	14.7	15.7	17.3	18.2	18.7
16.0	12.0	13.2	14.3	15.7	16.3	16.7
17.0	10.7	11.8	12.8	14.0	14.7	15.2
18.0	9.5	10.5	11.4	12.6	13.3	13.7
19.0	8.5	9.4	10.2	11.3	12.0	12.3
20.0	7.5	8.4	9.2	10.1	10.8	11.2

Note: Central axis depth doses for standard fields, using interchangeable cones. Field sizes are defined by the 80 per cent isodose level.

With SSD of 70 cm. or more, the isodose curves under irregular or oblique surfaces tend to parallel the skin surface. With short SSD, the variations in depth dose under the skin surface are significant and must be calculated (Fig. 4B).

7. ELECTRON BUILD-UP

With high energy photons, the dose at the skin surface is less than maximum because of the range of secondary electrons and the resulting build-up of dose at a

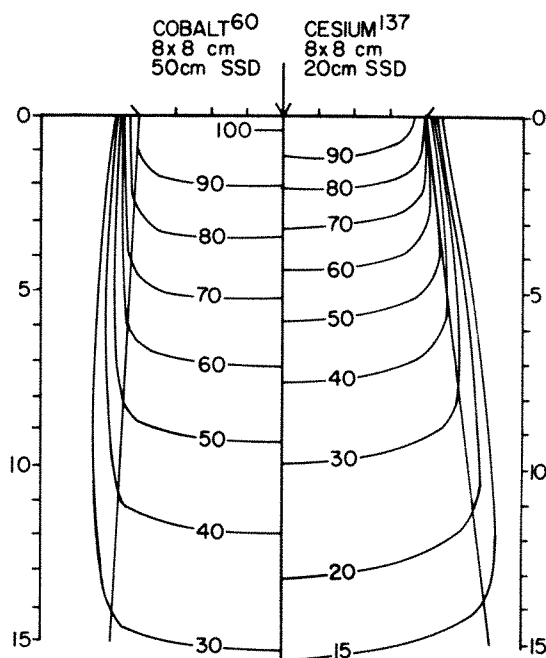


FIG. 2. *Isodose distributions.* With a 20 cm. SSD cesium 137 unit, the depth dose at 15 cm. is approximately one half of the depth dose of a 50 cm. SSD cobalt 60 unit. The divergence of the cesium 137 beam edges is easily seen. Sharpness of beam edges comparable to the cobalt 60 beam is achieved by use of "open" cone with secondary blocks close to the skin surface.

TABLE II
COMPARATIVE DEPTH DOSES

	250 kv. 3.0 mm. Cu HVL	Cesium 137 Magnetic Filtration		Cobalt 60		
Depth (cm.)	8×12 cm. 50 cm. FSD	8×12 cm. 20 cm. SSD	8×12 cm. 35 cm. SSD	8×12 cm. 35 cm. SSD	8×12 cm. 50 cm. SSD	8×12 cm. 70 cm. SSD
0.04	100	72	70	80	70	70
3.0	85.3	73.0	80.0	81.5	85.4	87.5
5.0	67.8	56.5	66.7	69.0	74.0	77.2
10.0	35.5	30.0	40.2	44.5	49.7	53.9
15.0	18.0	16.5	24.1	27.5	33.2	37.2

Note: Percentage of maximum dose at 0.04 mm., 3.0, 5.0, 10.0 and 15.0 cm. for different energies and source-skin distances allow ready comparison of the influence of voltage and source-skin distance.

depth. In addition to the primary beam, the superficial layers also receive contamination electrons generated in the source, its container, and the collimating device. These contamination electrons are partially absorbed in air.

Under optimal conditions, maximum electron build-up with cesium 137 occurs at approximately 1.3 mm. In clinical use, 90 per cent of the maximum build-up is reached at 0.4 mm. beneath the surface. By adding an electromagnet to remove contamination electrons, the build-up dose at 0.4 mm. can be reduced to 72 per cent of

the maximum. Under these optimal circumstances the build-up curve of the cesium 137 unit compares favorably with the cobalt 60 unit as commonly used in clinical practice (Fig. 5).

8. SKIN REACTION

The basal layer and superficial capillaries of the skin lie at an average depth of 0.4 mm. from the surface (Fig. 6).¹⁴ Capillary dilatation is considered the primary cause of erythema, while vesiculation and moist desquamation occur as a result of damage to the basal layer of the epidermis.

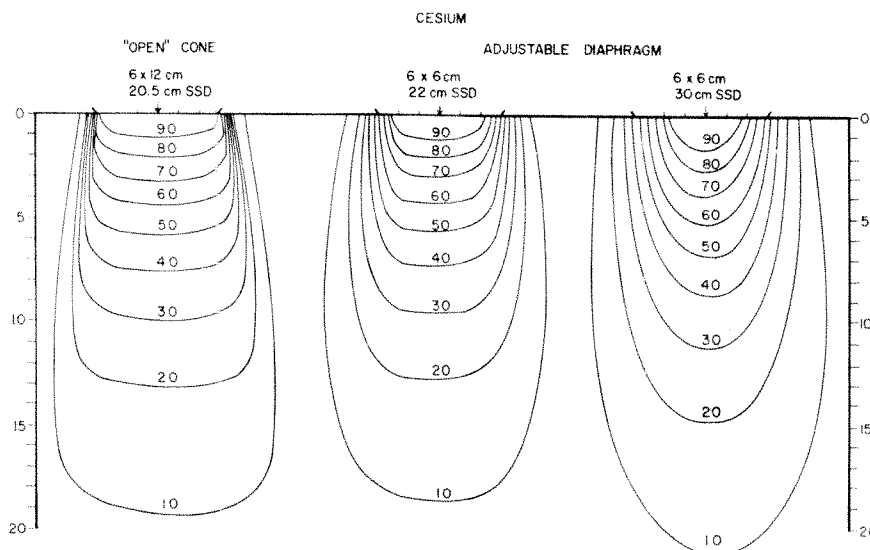


FIG. 3. Isodose distributions with SSD cesium 137. From left to right: "open cone" with fixed secondary blocks; adjustable diaphragm with no secondary blocks; same at longer SSD.

Skin reactions with cesium 137 were subjectively graded as mild erythema, brawny erythema, vesiculation, and moist desquamation. A type of reaction not seen with conventional energies (1 to 3 mm. Cu HVL) and rarely seen with higher energies has been designated "follicular," *i.e.*, erythema or vesiculation limited to the sites of the hair follicles (Fig. 8B). It is postulated that the invagination of the

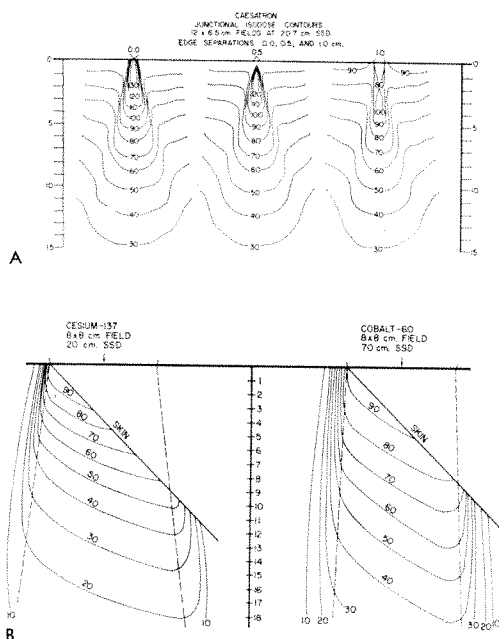


FIG. 4. (A) Functional isodose contours. With junctional fields, great care must be exercised to decrease in the measure possible the zone of overdose because of both penumbra and beam diversion. If the field edges are contiguous, there is a significant subcutaneous overdose extending for several centimeters depth. This overdose is less significant with edge separation but cold spots develop under the skin. Depending upon the depth of the disease to be treated, calculations must be made to know how much of an overdose can be afforded. For instance, for internal mammary chain lymph nodes, 1 cm. separation is adequate. There is no way to decrease the overdose from 5 cm. down except by prohibitive edge separation. (B) Contours for oblique fields. With high energy beams and SSD of more than 70 cm., the isodose curves have a tendency to run parallel to the surface of the skin. With short SSD, the isodose curves are not nearly as parallel to the skin surface and individual calculations must be made for irregular or oblique surfaces.

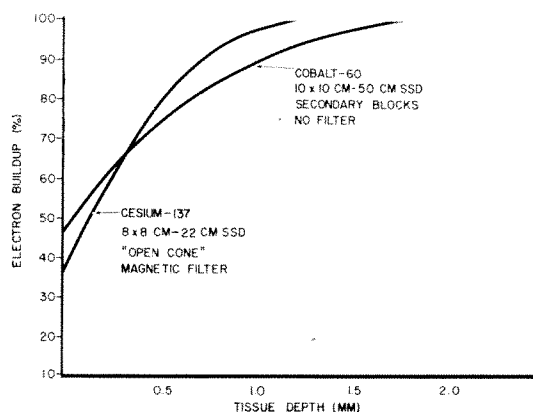


FIG. 5. Surface dose build-up for a cobalt 60 and a cesium 137 treatment field. Dose build-up beneath the surface of a cesium 137 beam (with optimal physical arrangement and electromagnetic electron decontamination) and of a cobalt 60 beam as commonly used in clinical practice. At the level of the basal layer of the epidermis (approximately 0.4 mm.) the build-up is comparable.

skin at these points exposes the sensitive levels to higher dose build-up, resulting in more marked reaction.

The influence of types of diaphragming and electromagnetic decontamination on skin reaction was studied in the patients having postradical-mastectomy irradiation to the internal mammary and supraclavicular lymph node regions. Increased skin reaction was noted when secondary blocking was added (presumably because of the addition of secondary contamina-

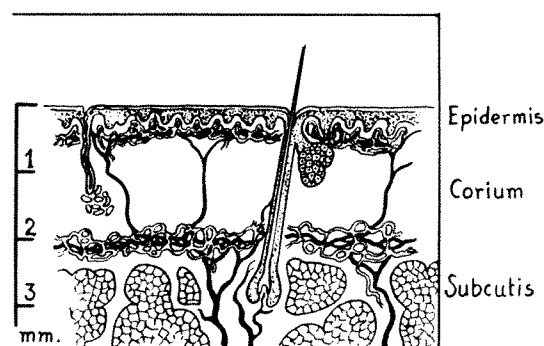


FIG. 6. Magnified cross-section of skin. The basal layer of the epidermis lies at a depth of approximately 0.4 mm. There is a downward extension of the epidermis at the hair follicles. (Reproduced by permission from *Acta radiologica*.¹⁴)

tion electrons); diminished skin reaction was noted with the addition of electromagnetic filtration.

Given doses of 6,000 rads in 28 days to the supraclavicular and internal mammary lymph node areas have produced erythema with occasional vesiculation in the region of the collar; these reactions subside within 2 to 3 weeks, leaving minimal residual pigmentation.

Areas about the head and neck and the chest wall have been irradiated with given doses ranging from 6,000 rads in 14 days to 8,000 rads in 31 days. Skin reactions were similar to those seen with comparable dosage using the cobalt 60 unit. In most cases erythema of varying degrees was observed.

Late skin changes and subcutaneous fibrosis in the patients followed for two years are similar to those seen with cobalt 60 therapy.

CLINICAL APPLICATIONS

The indications of this modality of radiation therapy are lesions located up to a maximum depth of 5 cm. under the skin, preferably 3 cm.

In Table III are summarized the anatomic distributions of the clinical material.

POSTRADICAL-MASTECTOMY IRRADIATION

The involvement of internal mammary chain lymph nodes in relation to the location and extent of primary breast lesions has been well established by extensive surgical series.^{5,15} Surgical removal of these lymph nodes benefits some patients in terms of five year survival, but no patient with lymph nodes greater than 1 cm. in diameter has survived five years.^{15,16} These surgical data justify an attempt to sterilize metastatic disease in the internal mammary chain lymph nodes by routine use of post-radical-mastectomy irradiation if the morbidity is not excessive.

The lymph nodes about the internal mammary vessels occupy a band of approximately 4 cm. in width, centered over

TABLE III
ANATOMIC SITES IRRADIATED BY CESIUM 137
(275 Patients)
May, 1959 to May, 1961

Breast	Postradical-mastectomy irradiation of supraclavicular and internal mammary chain lymph nodes	87	115
	Irradiation of internal mammary chain lymph nodes only with cesium 137 unit in combination with irradiation with cobalt 60 unit of axilla, supraclavicular regions, and chest wall	28	
Lymph nodes (almost all neck lymph nodes) ..		46	
Parotid.....		11	
Auditory canal.....		4	
Oral cavity primaries.....		9	
Additional localized therapy for primary oral cavity or oropharynx lesions and metastatic neck lymph nodes.....		69	
Miscellaneous.....		21	

the lateral border of the sternum at an average depth of 3 cm. (Fig. 7A).^{5,6,15} Metastases to the opposite internal mammary chain are uncommon.¹⁶

The treatment fields encompassing the lymph nodes of the apex of axilla, supraclavicular region and internal mammary chain are shown in Figure 7B.

Effective tumor dose levels for breast cancer are not well established. Reports of Lumb,¹⁰ Williams and Cunningham¹⁷ and Friedman and Pearlman⁷ suggest that tumor doses in the range of 4,000 to 4,500 rads in 4 weeks are effective in most cases. Parasternal recurrences were observed by Smithers and Rigby-Jones¹² in 65 cases, of which only 4 had received postoperative irradiation. Tumor doses in the range of 3,500 r had been given in the cases where there was no parasternal recurrence.

With 250 kv. (3 mm. Cu HVL) skin tolerance limits the skin dose in 3 weeks to 4,000 rads to the supraclavicular, and to 4,500 rads to the internal mammary chain field. Taking into account bone absorption, the tumor dose is from 3,500 to 3,800 rads. Moist desquamation is frequently seen (Fig. 8B). Esophagitis and tracheitis, and

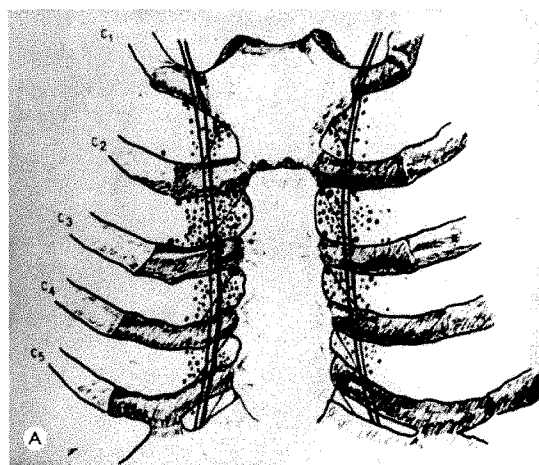
radiation pneumonitis of varying degrees are the rule. Lung fibrosis of moderate degree (usually asymptomatic) appears in a high percentage of cases. Varying degrees of skin atrophy, scarring, and telangiectasia are expected sequelae.

The limitation of skin reaction is no longer present with supervoltage units, but because of increased depth doses, there is a proportionately greater reaction in the underlying structures.^{2,3} The rapid inverse square fall-off of the short SSD units may minimize the pulmonary and mediastinal fibrosis. Doses at the skin surface level of maximum build-up, and at 10 cm. depth, are given in Table IV in reference to tumor dose at a depth of 3 cm.

With the cesium unit, the lymph node dose is approximately 80 to 90 per cent of the dose in the supraclavicular area and 75 per cent to the internal mammary chain area. Originally, 5,400 rads (300 rads given dose daily) were delivered in 3 weeks. Because the skin reaction, tracheitis, and esophagitis were minimal, the dose was increased to 6,000 rads in 20 treatments. To ensure a better coverage of the internal mammary chain lymph nodes, the width of the internal mammary chain field was enlarged from 6 to 8 cm.

When 5,400 rads are delivered, an occasional, barely detectable pneumonitis, entirely asymptomatic, develops 3 to 6 months after treatment. With 6,000 rads given through a 6 cm. wide portal, a limited pneumonitis, as a rule mildly symptomatic, will occur in most cases, evolving later in a thin parasternal streak of radiation fibrosis. With an 8 cm. wide portal, tracheitis and esophagitis were more severe and symptomatic pneumonitis developed in all cases. The 8 cm. width was abandoned.

The present policy for patients with a high probability of involvement of the internal mammary chain lymph nodes (inner quadrant of subareolar lesions with positive axillary lymph nodes, or outer quadrant lesions with multiple axillary lymph nodes positive in the operative specimen)



POST MASTECTOMY FIELDS
CESIUM 137

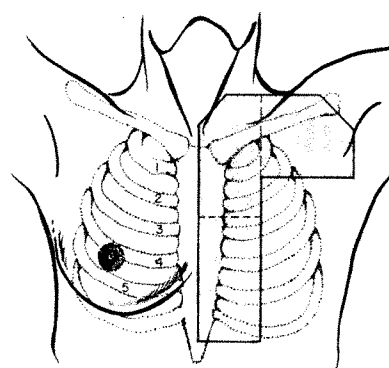


FIG. 7. (A) *The internal mammary lymph nodes.* These are distributed along the internal mammary vessels and centered near the lateral border of the sternum. (Reproduced by permission from *Journal international de chirurgie*.⁵) (B) *Postoperative irradiation. Field arrangement for post-radical-mastectomy irradiation of internal mammary and supraclavicular lymph node areas.* The internal mammary fields are 6 cm. in width and encompass the fifth intercostal space inferiorly. Limitation of field sizes at short SSD requires a multiple field technique.

is to give 6,000 rads (4,500 rads TD); in the other (small inner or subareolar lesion with no involvement of axillary lymph nodes, or outer quadrant lesions with few axillary lymph nodes involved) 5,400 rads (4,000 rads TD) are given.

In the patients receiving preoperative radiation to the breast and the surrounding lymphatics, or in the patients being



FIG. 8. (A) Skin reaction following irradiation with 250 kv. (3 mm. Cu HVL). Given doses of 4,000 rads to the supraclavicular area and 4,500 rads to the internal mammary chain area were delivered in 21 days. (B) Skin reaction following irradiation by SSD cesium 137. A given dose of 6,000 rads to the supraclavicular and internal mammary areas was delivered in 28 days. The follicular reaction is typical. The skin reaction is less where adjacent fields have been separated to reduce high dose areas beneath the skin.

treated entirely with external irradiation on the cobalt 60 unit, if the separation of the tangential fields is more than 20 cm., the internal mammary chain is not in-

cluded in the tangential portals. It is irradiated by a straight-on field. The cesium 137 unit is preferable to the cobalt 60 unit for the internal chain field.

TABLE IV
INTERNAL MAMMARY FIELD PERCENTAGE DEPTH DOSES
(Normalized to 100% at 3 cm. Tumor Level)

	250 kv.* 16×6 cm. 50 cm. FSD	Cesium 137** 12×6 cm. 20.5 cm. SSD	Cobalt 60 12×6 cm.		
			35 cm. SSD	50 cm. SSD	70 cm. SSD
0.04 cm.	124	100			
Maximum	124	137	98	83	81
3.0 cm.	100	100	123	118	115
10.0 cm.	41	42	100	100	100
			53	57	61

Note: Percentage of depth doses, using different techniques for irradiation of the internal mammary chain, has been normalized to 3.0 cm. to allow ready comparison of skin and deep structure doses in relation to tumor dose at that level.

* Technique previously used was 3.0 mm. Cu HVL; the correction for elongation and bone absorption (3%) is included.

** Technique now in use.

HEAD AND NECK

Short SSD teletherapy for patients with head and neck squamous cell carcinomas has been well established by 30 years experience with telerradium units.

A single homolateral portal, parallel opposing portals, or paired wedge portals with kilocurie cobalt 60 units or 2 to 6 mev. roentgen-ray generators produce volume distributions superior to those obtained with short SSD teletherapy units for tumors of the oropharynx, nasopharynx, and some of the extensive lesions of the oral cavity. Likewise, long SSD units have an edge of superiority for the irradiation of the tumors of the larynx and hypopharynx because one can neglect the obliquity and the irregularity of the skin surface and use, as in the irradiation of vocal cord tumors, one single homolateral portal with an ideal volume distribution. Also, the management of the neck lymphatics, in particular the lymphatics of the lower neck, can be carried out simply by one single anterior split field.

However, there are, in the head and neck area, asymmetrically located lesions such as those of the gingivobuccal sulci, alveolar ridges, buccal mucosa, middle ear, parotid area and some metastatic neck lymph nodes, where a single homolateral portal with a beam that has a fast fall-off of dose is the simplest planning next to an electron beam. The treatment may be carried out entirely with the cesium 137 unit at 20 to 25 cm. SSD, or in combination with interstitial gamma-ray or intraoral cone therapy.

There are also other clinical situations where one can make good use of the combination of fast fall-off of dose and skin sparing. For instance, at the end of 5,000 to 6,000 rads tumor dose delivered with a long SSD cobalt 60 unit to a tumor of the tonsil or the glossopalatine sulcus, additional localized therapy can be delivered to an asymmetrically located residuum. Recurrences in the parotid area from nasopharynx cancers were palliated effectively with no noticeable mucositis in the pharynx.

The planning of some of the commonly

encountered situations is briefly outlined:

1. *Asymmetric lesions, primarily in the oral cavity.* Seven thousand to 8,000 rads (given dose) with daily given doses of 300 rads are delivered in 5 to 6 weeks. The tumor dose is from 5,000 to 6,000 rads depending upon the depth of the lesion. A bite or intraoral mold, containing a sheet of lead of the one-half value layer, can be made adding significant protection to the opposite side of the oral cavity. An additional interstitial gamma-ray implant can be used to deliver 2,000 to 3,000 r if the lesion has not completely regressed at the end of the external beam treatment. A moist desquamation may develop, but, because it is produced in part by the superficially absorbed contamination electrons, it heals fast and does not result in chronic changes similar to those following a moist desquamation produced by 200 to 250 kv. roentgen rays.

Recurrences in the skin flap following a surgical resection, which are asymmetrically located, can be handled with the same geometry and dosage as primary lesions.

2. *Lesions of the parotid gland and middle ear.* A single homolateral portal is used with a total given dose of 6,000 to 7,000 rads in 4 to 5 weeks (300 rads daily given dose) either pre- or postoperatively, or as the only therapy.

3. *Additional localized therapy.* After a tumor dose of 5,500 to 6,000 rads has been given in 5 to 6 weeks to lesions of the oropharynx or oral cavity and a residuum of induration is still felt asymmetrically, an additional 1,000 to 1,500 rads can be given with the cesium 137 unit over a reduced field covering the residuum.

After heavy irradiation of large lymph node areas, if there are still some residual palpable lymph nodes and a neck dissection is not contemplated, doses of 1,000 to 1,500 rads are given in 4 to 5 days.

4. *Recurrences of the nasopharynx cancers in the parotid lesions* are not uncommon and have been given 5,000 rads (given dose) in 3 weeks without producing significant skin reaction and mucositis in the oropharynx mucous membrane.

5. *Recurrent neck nodes after a radical neck dissection.* Six thousand rads (12×500 rads given dose) are delivered to small fields covering only the lymph nodes. The same geometric planning and dosage can be used for postsurgical recurrences following a commando procedure if the recurrence is located over an area which is not over a vital structure, for instance the stump of the mandible. In that instance, 7,000 rads may be given in 3 weeks.

6. *Preoperative irradiation of neck lymph nodes.* If there are palpable lymph nodes when a primary oral cavity lesion is treated by an interstitial radium implant, or if metastatic lymph nodes appear later and are 3 cm. or more in diameter, a dose of 5×800 rads (given dose) to a field covering only the palpable lymph nodes is given preoperatively and 10 days later a radical neck dissection can be carried out.

CONCLUSION

Cesium 137 permits the design of a compact unit for short distance teletherapy with high dose rates, large fields, sharp beam edges, and single collimation. Such units have a place in the armamentarium of radiotherapy for the treatment of patients with lesions located beneath the skin to a depth of 5 cm.

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A CESIUM HEAD AND NECK UNIT*

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TELECURITHERAPY may be defined as the application of a canalized beam of gamma radiation to the treatment of disease. Although telecurietherapy is almost as old as radiotherapy, a general and widespread interest in this form of radiation treatment has become manifest only since adequate quantities of suitable artificial radioactive isotopes have become available during the past fifteen years.

Few will, nowadays, dispute the physical and technical advantages of telecurietherapy over conventional 200 kv. radiation. Yet it would seem that as far as the treatment of most accessible cancers of the head and neck is concerned, there is as yet little evidence to show that the results obtained by the use of the post-war telecurietherapy units are very much better than those obtained with the more modest pre-war equipment.

As there is a distinct dearth of telecurietherapy equipment, the design of which is based upon previous clinical experience, it was felt that, as this form of treatment had been in constant use at the Royal Marsden Hospital for over thirty years, the special experience so gained would justify an attempt to design a unit for the treatment of head and neck cancer which would incorporate such technical features as experience had shown to be of importance.

FORMER HEAD AND NECK TELECURIETHERAPY UNITS

At the Royal Marsden Hospital, the use of telecurietherapy has been restricted mainly to the treatment of cancers of the head and neck since the radioactive sources hitherto available have been relatively small quantities of radium (5-12 gm.) or in recent years small quantities of cobalt (5-15 c). Treatment has of necessity been restricted to neoplasms affecting the larynx, the laryngopharynx and oropharynx and

the mouth. Tumors of the nasopharynx and paranasal sinuses were not treated because they were either situated beyond the useful range of the apparatus or protection of the eye was impossible.

Since 1936 an apparatus of the radium beam research unit pattern¹ containing a radium source has been in continuous use; a second unit of this type containing a cobalt source was added in 1952.² After eight years of comparative use it became obvious there was little clinical difference between cobalt and radium, the reactions, if anything, being slightly less with cobalt. One year ago the radium source was permanently replaced by cobalt.

From a purely physical point of view, apparatus of this kind has little to recommend it. The output is low (16 r/min.), the depth dose is poor ($d_{\frac{1}{2}}$ 3.5 cm.) and the edge of the beam is ill-defined. By modern standards such equipment would clearly be regarded as obsolete. Nevertheless some 4,000 patients with head and neck cancer have been treated by equipment of this kind with results that are by no means negligible.

That such apparatus could be put to satisfactory clinical use depended on the fact that no attempt was made to imitate technically treatment by conventional 200 kv. roentgen rays. On purely physical grounds, this type of telecurie unit could not stand comparison with 200 kv. roentgen equipment and, therefore, an entirely different technical approach had to be adopted so as to try to turn to profit its apparent physical disadvantages. This was done by:

(1) Strict selection of cases. Treatment was limited to superficial accessible malignant epithelial tumors of the head and neck, where relatively small volumes of tissue had to be irradiated. Widely spreading radiosensitive tumors such as the sar-

* Presented at the Forty-third Annual Meeting of the American Radium Society, Colorado Springs, Colorado, May 11-13, 1961.

comas of lymphoid tissue were treated by roentgen-ray therapy, which was also employed when pure palliation was necessary.

(2) The poor percentage depth dose meant that crossfire techniques using multiple small fields were essential if a reasonable dose were to be built up at a depth, and, as homogeneous distributions were extremely difficult to achieve by this method, inhomogeneity had to be accepted.

(3) The poorly defined divergent edge of the beam, although not in a strictly physical sense a penumbra, acted as such from a practical point of view; and since it could not be eliminated provision had to be made for its useful employment.

It was soon appreciated that percentage depth dose and penumbra were related to each other in a complementary fashion and that the angulation of beams of radiation to each other and the overlapping of adjacent beam edges never gave rise to excessive or dangerously high zones of overdosage. This fortunate effect was not deliberately sought but was an incidental consequence of the physical factors imposed by the original use of small quantities of radium as the source of gamma radiation and the short source skin distances that were unavoidable if the output was to be at all reasonable for routine clinical use.

The production and use of an inhomogeneous distribution of radiation, comprising very often a series of discrete localized regions of high dose ("hot spots"), would seem to involve risks of underdosage and recurrence, or overdosage and necrosis, but in practice homogeneity did not seem to be important and, were this not so, our form of telecurietherapy could never have survived.

(4) Having once accepted the value of an inhomogeneous radiation distribution, the next obvious step was to attempt to relate this to the natural history of the disease being treated.³ After a period of many years of study, it became possible to detect certain patterns of behavior among the tumors of the various sites treated, and with this knowledge it became possible to relate the

radiation distribution to the behavior of a particular tumor.⁴

NEW CESIUM UNIT

Taking this into account and above all being conscious of the limitations of our particular telecurietherapy apparatus, we set ourselves the problem of designing a new one that would eliminate as many as possible of the disadvantages of the old and yet still retain those features which enabled us to adapt the technique to the disease. This seemed to us very necessary since much modern equipment has been designed by the physicist and engineer which leaves the radiotherapist little choice but to try and fit the disease to the machine.

The main principles underlying the design of the new unit are: (1) safety; (2) mobility; and (3) because most of the tumors in the head and neck are relatively superficially placed, a poor percentage depth dose has been deliberately selected. Moreover, to allow for the differences in the depth of tumors below the surface of the head as opposed to the neck, the apparatus has been constructed so that one part is devoted to the treatment of cancers arising between the base of the skull and the hyoid bone (head end) and the other part designed so as to treat tumors arising between the hyoid bone and the clavicles (neck end). The apparatus is, therefore, of "Janus" type or two faced, the beam of radiation from each end having its own physical features (Fig. 1).

THE HEAD END

The fields are determined by means of a light device, the range being 12×12 cm.— 4×4 cm. The $d_{\frac{1}{2}}$ is 7 cm. and the output at 30 cm. source skin distance is 15 r/min. The 80 per cent isodose surface delineates the geometric edge of the beam. Provision has been made for beam direction and "indirect" protection⁵ by the interposition of lead blocks in the beam of radiation so as to shield an organ such as the eye or produce an irregularly shaped field. This end is used for neoplasms of the

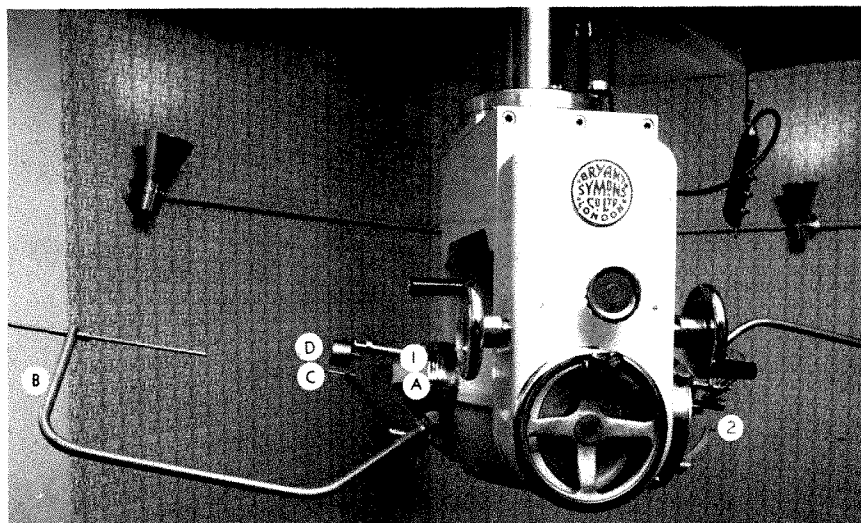


FIG. 1. The "Janus" type telecesium head and neck unit. (1) Neck end with (A) treatment cone, (B) beam director, (C) source skin distance pointer and (D) lead cylinder for ocular protection. (2) Light device used for head end. A similar range of attachments is available.

nasopharynx, tonsil, fauces, base of tongue, paranasal sinuses, and orbit.

THE NECK END

Interchangeable cones are used for treatment, with field sizes of 4×4 cm., 7×5 cm., 8×5 cm., and 6×5 cm. The $d_{1/2}$ is 5 cm., the output 33 r/min. at 20 cm. S.S.D. and the 80 per cent isodose curve is again selected as identifying the geometric edge of the beam. This end is used for cancers of the buccal cavity and the laryngopharynx, larynx and for cervical lymph node metastases. It has been designed, and shaped so as to permit irradiation of the root of the neck without coming in contact with the shoulder of the patient lying on a couch. Direct and indirect beam protection is available.

There is no indication for using wedge filters with this apparatus since the depth dose is too low and the skin sparing effect would be lost.

An apparatus of this kind could be of value to radiotherapists who are called upon to treat a considerable number of patients with head and neck cancer. Although the techniques outlined could be dangerous if used with a modern kilocurie cobalt source utilizing a long source skin distance, a kilocurie cobalt apparatus could be de-

signed according to the principles mentioned above.

From our experience with both this unit and a larger unit containing 1,500 c cesium, we believe that this particular isotope could be replaced with advantage by cobalt since, apart from any physical advantages it may possess as a source of gamma radiation, the reactions obtained with cesium therapy are much more marked than those seen with cobalt, resembling in many respects those seen when using 250 kv. radiation.

SUMMARY

Telecurietherapy has been in constant use at the Royal Marsden Hospital for thirty years. For the past twenty-five years the apparatus has remained unchanged, but the original radium source has been replaced by a cobalt one. The quantities of radioactive material used have been small (5–12 gm. radium, 5–15 c cobalt) and the source skin distance short (8.3 cm.). The inevitable penumbra has been accepted and its problems solved clinically. Based on an experience obtained in the treatment of some 4,000 head and neck tumors, a new apparatus has been designed so as to remedy some of the disadvantages in-

herent in the older apparatus, and to adhere to the principle that the machine should always be adapted to the disease being treated with no attempt made to adapt the disease to the machine.

The new unit consists of two treatment ends, one for tumors arising in the region of the head and the other for those arising in the neck. Different treatment factors have been selected for each treatment end. The writer believes that cesium is inferior to radium or cobalt as a source of gamma radiation as judged by the clinical responses of the irradiated tissues.

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The apparatus described here was designed in association with Mr. J. C. Jones, M.A., F.

Inst. P., Physicist, Royal Marsden Hospital, and Mr. E. W. Savage of Messrs. Bryant Symons.

A full account of this unit is to be published in the near future.

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COMMON MEDICAL PROBLEMS IN RADIOTHERAPY PATIENTS*

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FOR the last six years a member of the Department of Medicine has been assigned to participate in the in-hospital care of radiotherapy patients. This assignment grew out of the fact that the Department of Radiotherapy, as one of the three therapeutic arms of Memorial Hospital, assumes clinical responsibility for patients undergoing radiotherapy. The representative of the Department of Medicine and an Attending radiotherapist jointly conduct rounds on all service cases assigned to the radiotherapy beds in James Ewing Hospital of Memorial Sloan-Kettering Cancer Center three to four times a week. The radiotherapy residents are assigned in rotation to care for these patients and attend rounds regularly.

The following case history is presented as an example of the combined medical-radiotherapy problems which arise and are managed on these rounds.

CASE 1. A.K., a forty-four year old white female, had a radical mastectomy in January, 1954 and remained well until 1957, at which time chest wall recurrence was found as well as skeletal metastases. A bilateral oophorectomy was performed with a remission of the disease for six months at which time the nodules on the chest wall started to grow again. The patient was started on prednisone with subjective relief of pain and objective regression of the tumor. Therefore, a bilateral adrenalectomy was performed. She was maintained on 75 mg. of cortisone a day for six months when rapid progression of her disease was noted. She was referred for irradiation and a course of treatment with the betatron, using 10.4 mev. electrons through an anterior 15×15 cm. field, was started. It was planned to give approximately 4,000 r. However, when the patient was about half way through her therapy, she developed increased weakness, epigastric distress, nausea,

vomiting and was admitted to the hospital as an emergency. On admission the patient appeared to be acutely ill, pulse was 128, blood pressure 60/0, blood urea nitrogen 25.5, chlorides 96, CO₂ 20, sodium 126, potassium 5.87 (Table I).

Treatment was started with 100 mg. of hydrocortisone sodium succinate (solucortef) intravenously and 50 mg. of cortisone intramuscularly every eight hours. Glucose in saline was administered intravenously. Forty-eight hours later there was a complete remission of the symptoms. Blood pressure was 102/80, blood urea nitrogen 20, chlorides 102, CO₂ 24, sodium 134, potassium 5.3. Radiotherapy was continued to the anterior chest wall according to the previously decided treatment plan. The patient was discharged on 37½ mg. of cortisone every eight hours by mouth and completed this course with satisfactory improvement.

The recognition and adequate treatment of the iatrogenic adrenal insufficiency in a patient who had had ablative hormonal therapy for metastatic breast carcinoma permitted the successful completion of her radiotherapy.

In the years 1956 through 1960 there were 889 admissions to the beds assigned to the radiotherapy department in James

TABLE I
ELECTROLYTES IN PATIENT WITH IATROGENIC
ADRENAL INSUFFICIENCY

Case 1 (A.K.). Forty-four year old Female—
Cancer of the Breast

	Blood Urea Nitrogen	Hct.	Na	K	Cl	CO ₂
On admission	25.5	47	126	5.87	96	20
Forty-eight hours later	20.0	43	134	5.30	102	24
One week later	15.4	42	135	5.31	101	24

* From the Departments of Medicine and Radiotherapy, Memorial Sloan-Kettering Cancer Center, New York, New York. Presented in Part at the Forty-first Annual Meeting of the American Radium Society, Hot Springs, Virginia, April 6-8, 1959.

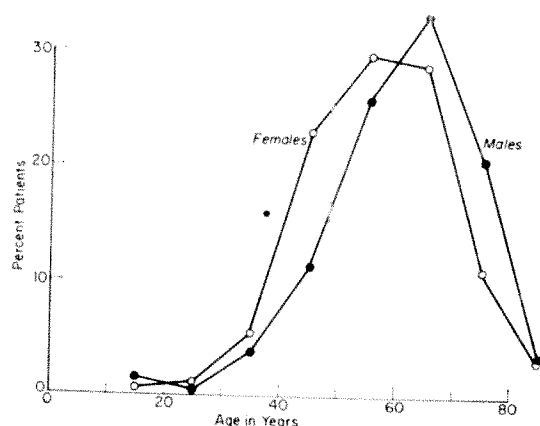


FIG. 1. Age distribution of hospitalized patients on the Radiation Therapy Service from 1956 to 1960.

Ewing Hospital. There were twice as many females as males. Seventy-five per cent of the patients were over the age of fifty and on average the males were approximately ten years older than the females (Fig. 1).

These cases represent a group of seriously ill patients who required intensive medical care. The vast majority was in the hospital primarily because they were too ill to complete the prescribed course of radiotherapy on an out-patient basis. This is distinctly different from the nature of the surgical services of the same institution, where most patients are admitted for definitive operative procedures and represent the best medical candidates for surgery. The consequences of the surgical procedure itself constitute the major problems to be faced by the attending and resident staff. On the radiotherapy beds, on the other hand, the patients represent problems requiring constant medical care.

The medical problems seen in these patients can be divided into three major categories: (1) those which are associated with this particular age group, *i.e.*, geriatrics problems; (2) those which are associated with particular types of tumors, which are referred to radiotherapy for definitive or palliative therapy (Table II); and (3) those which arise as a consequence of this modality of therapy. During the five years of this study there were 955 medical

TABLE II

TUMOR DISTRIBUTION OF PATIENTS HOSPITALIZED ON RADIOTHERAPY SERVICE (JAMES EWING HOSPITAL) 1956-1960

Type of Tumors	
Gynecologic.....	220
Head and Neck.....	102
Breast.....	158
Gastrointestinal.....	99
Lung.....	69
Skin, soft tissue and bone.....	45
Genitourinary.....	31
Miscellaneous.....	50
Metastatic; primary?.....	22

problems which are usual to a geriatric population. Nine hundred and thirty-five problems arose out of cancer or were associated with the cancer for which the patients were receiving therapy and 248 arose as a consequence of this modality of therapy (Table III).

GERIATRIC PROBLEMS

Cardiovascular, pulmonary complications made up the largest segment of the geriatric problems. One of the most frequently encountered difficulties was the problem of rehydration of a debilitated patient with a restricted cardiovascular reserve. A constricted circulating blood volume produces problems due to the drop in the glomeruli filtration rate, elevated blood urea nitrogen and metabolic acidosis. Overzealous rehydration of the patient could result in congestive heart failure and pulmonary edema. Therefore it is necessary to adjust the fluid intake cautiously, on a day to day basis.

A second problem pertaining to the cardiovascular system relates to the maintenance of adequate digitalization. In the

TABLE III

MEDICAL PROBLEMS IN RADIOTHERAPY PATIENTS 1956-1960

Geriatric.....	955
Cancer.....	935
Radiotherapy.....	248

presence of hypokalemia, digitalis toxicity may become evident before adequate digitalization has occurred. In patients receiving radiotherapy where total body potassium stores may have been depleted by anorexia, inadequate food intake or nausea and vomiting, the added burden of radiotherapy may enhance this depletion by producing more nausea, vomiting and/or diarrhea. At this point, digitalis toxicity also may contribute to the nausea, vomiting and diarrhea. Unless all these factors are carefully sorted out and handled individually, the prescribed course of radiotherapy may have to be interrupted unnecessarily.

During the last ten to fifteen years, the problem of infection has become increasingly difficult to manage. Not only is each institution harboring strains of resistant staphylococci, but an increasing number of upper respiratory and wound infections due to beta streptococci and diphtheria is appearing as well.

In the management of these problems three basic points stand out:

1. The use of "prophylactic antibiotics" creates more problems than it prevents. It should be avoided.

2. The identification of the responsible microorganisms and their sensitivities should be undertaken as frequently and as soon as possible. Antibiotics would be chosen on the basis of this information. "Prefabricated" mixtures are generally less effective than "tailor made" combinations prescribed on the basis of *in vitro* studies.

3. Microorganisms apparently can mutate faster than pharmaceutical chemists can produce new antibiotics. Therefore it is necessary to return to first principles of basic cleanliness, sterility and isolation. This can do much to decrease infection rates in most institutions.

CANCER PROBLEMS

The most frequent problems associated with cancer *per se* were in the field of nutrition. Fluid and electrolyte imbalances, malnutrition and avitaminosis were the

dominant problems. In another publication electrolyte imbalances most frequently seen in patients undergoing radiotherapy were reviewed.¹ In that publication it was shown that those electrolyte imbalances most frequently occurring in cancer patients included metabolic acidosis due to renal shutdown, respiratory alkalosis and metabolic acidosis secondary to hepatic coma, metabolic acidosis secondary to adrenal insufficiency and metabolic acidosis secondary to diabetes.

One hundred and fifty-four patients had either overt diabetes or an aberration of carbohydrate metabolism consistent with the diagnosis of diabetes. These findings are in keeping with the previously described association of diabetes and cancer.²

The case discussed at the beginning of this paper is one that would be typical of the adrenal insufficiency adrenal crisis syndrome which has been seen in patients receiving radiotherapy. During this five year period adrenal crisis was seen in eight patients who had been on adequate maintenance of adrenal steroid following adrenalectomy and/or hypophysectomy for metastatic carcinoma of the breast. The institution of a course of radiotherapy necessitated an increase in their maintenance steroid. When this was overlooked, the patients became seriously ill, resulting in interruption of their prescribed radiotherapy. In each instance increasing the maintenance steroid allowed for the orderly progress of the previously decided treatment plan.

RADIOTHERAPY PROBLEMS

It is impressive to us that medical problems solely attributable to the radiotherapy have developed infrequently. Less than 15 per cent of the patients developed anorexia, nausea and vomiting as a consequence of the radiotherapy. It appears to us that perphenazine (Trilafon) is conspicuously more effective than the other anti-emetic agents currently available. However, an orderly double-blind evaluation of all drugs in this area is yet to be done.

The medical problems associated with the radiotherapy *per se* frequently revolved about the nutritional status of the patient. Hypochloremic alkalosis from vomiting, potassium depletion alkalosis from inanition and hypochloremic acidosis from diarrhea were the three most frequently seen in electrolyte imbalances.

Because of our interest in the possibilities of modification of late radiation changes, many patients with old radiation injuries were referred to our group at Memorial Center. Some of these have been admitted to the hospital for medication and evaluation prior to the initiation of an investigative study. Forty-four patients have been admitted in the five year interval reported here. In this clinical study two-thirds of the patients with ulcers and fibrosis of two to thirty years' duration have shown good to excellent improvement on the thyroid analogues L-triiodothyronine and triiodothyropropionic acid.³

Patients undergoing radiotherapy to large segments of the trunk have a decreased ability to tolerate infections. As pointed out earlier, the increasing number of uncontrollable infections has taken on serious proportions. These infections relate not only to the resistant staphylococci but gram negative bacilli of colonic or persistent chronic renal infections resistant to most therapeutic regimens. It is not surprising therefore that in all three categories of problems, over 200 patients seen during this five year period had serious infections. Four cases of subacute bacterial endocarditis due to gram negative rods were seen. Twenty-two patients were admitted because of serious uncontrollable infection, 14 of whom succumbed to this complication.

Forty-six patients developed hematologic problems secondary to their irradiation. Since many patients received a chemotherapeutic agent prior to or following irradiation, it has been difficult to define the role each is contributing to the hematologic depression. However, in these 46 cases none received a chemotherapeutic agent known to have a marrow suppressive action

but appeared to be related to the radiotherapy which they were receiving.

During the five years of this study it has become apparent that medical problems with a multitude of symptoms and signs are frequently attributed to the radiotherapy without further investigation. After an orderly history, physical examination and pertinent laboratory studies, many conditions such as intestinal obstruction, perforated ulcer, adrenal insufficiency, drug toxicity, extension of metastatic disease, intracranial metastases, and hypercalcemia, have been found to be the underlying cause of the patient's illness. Thus, when the physician takes the time to listen to the patient's complaints and analyzes them in the light of the whole disease pattern, it becomes apparent that medical problems directly related to the radiotherapy constitute approximately 10 per cent of all the medical problems the patients present. The following case history illustrates the dangers inherent in attributing to the radiotherapy all the untoward symptoms the patients manifest.

CASE II. Patient C.G., a fifty-one year old female, was treated by intravaginal radium for carcinoma of the endometrium at another institution in 1957. In 1958 she was admitted to Memorial Center because of profuse vaginal bleeding and severe dyspnea. At the time of her admission to the hospital, the patient weighed over 325 pounds. Physical findings included marked edema of the lower extremities and the back, and a left pleural effusion. The heart was diffusely enlarged and murmurs consistent with mitral stenosis, mitral insufficiency, aortic stenosis, and tricuspid insufficiency were present. The rhythm was that of auricular fibrillation. The liver was palpable five fingers below the costal margin. The spleen was not palpable (Fig. 2).

An endometrial aspiration was positive for malignant cells consistent with the diagnosis of endometrial carcinoma. It was evident that the adequate management of her endometrial carcinoma would have to wait until the patient had had her congestive heart failure corrected. Therefore, the patient was digitalized and maintained on .2 mg. of digitoxin daily. A

diuretic regimen of Luckey was instituted consisting of ammonium chloride, Diamox and mercurhydrin in appropriate sequence with very gratifying response. The patient lost 150 pounds in a period of twelve weeks (Fig. 3). At this time it was decided to institute radiotherapy to the pelvis utilizing a cobalt 60 source. When a dose of approximately 1,000 rads had been achieved, the patient developed rather severe nausea and vomiting. A diagnosis of radiation sickness was tentatively made. However, electrocardiographic findings at this time indicated a complete atrioventricular dissociation and marked depression of the ST segment. The patient on closer questioning also complained of some ringing in her ears. The digitalis was discontinued and potassium was administered by mouth and intravenously because the patient's serum potassium level had inadvertently fallen to 3.5 mEq. per liter during the rigorous diuretic regimen. With adequate replacement of her potassium stores and a revised digitalis maintenance, the patient's nausea and vomiting disappeared and the radiotherapy was continued.

The diuretic regimen at this time was changed from Diamox to include chlorothiazide. A week later when a dose of 1,480 rads had been delivered, the patient developed petechiae and hematuria. The platelet count was 25,000. Prior to the initiation of radiotherapy the platelet count had been 175,000. Again a tentative diagnosis of radiation induced thrombocytopenia was entertained. Examination of the patient's clotting mechanisms was undertaken and it was found that they were all essentially normal. However, in studying the platelet function,

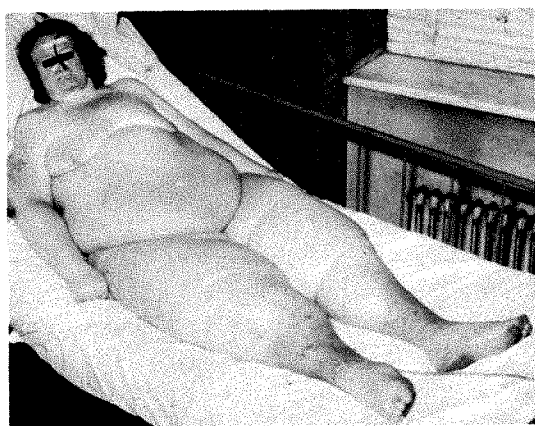


FIG. 2. Case II. Obese woman with cardiac decompensation.

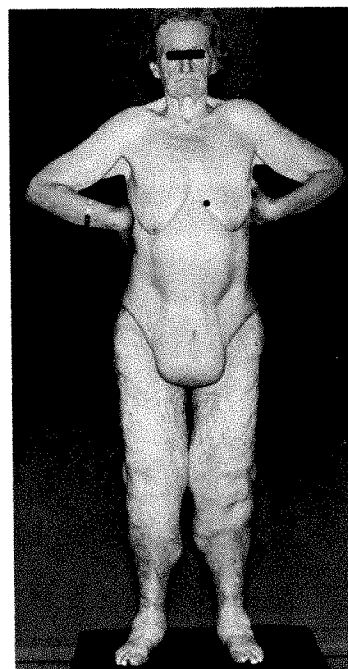


FIG. 3. Case II. Twelve weeks after medical treatment. The patient lost 150 pounds.

it was found that the patient had an auto-agglutination of her platelets probably due to one of the medications she was receiving. It was found on later study that diuril was the culprit and not radiotherapy. Upon removal of the chlorothiazide from the diuretic regimen and the addition of 6 methyl-delta-1-hydrocortisone (Medrol) the patient's platelet count rose steadily to over 100,000 in two weeks.

Upon completion of the radiotherapy, the patient was discharged from the hospital improved and during the last eighteen months has been seen intermittently, primarily for her cardiac problem. Repeated endometrial aspiration has been negative for malignant cells.

In the same patient on two occasions, medical complications have been attributed to the radiotherapy, but on investigation were found to be due to drug toxicity. Upon the recognition of this fact, the orderly progress of her radiotherapy continued. It is our opinion that radiation sickness is a diagnosis of exclusion. Its inclusion in an orderly differential diagnosis may be pertinent but it should be listed last, not first, as is all too frequently the case.

CONCLUSIONS

The in-patient population of the Radiotherapy Department of James Ewing Hospital of the Memorial Sloan-Kettering Cancer Center represents the most seriously ill patients who are receiving radiotherapy. Only 10 per cent of the medical problems are an outgrowth of the radiotherapy. Ninety per cent are related either to the cancer or the concomitant geriatric medical problems seen in this age group.

In most American institutions the training program in radiotherapy has not stressed the day to day management of patients with cancer. However, those who are performing the fundamental therapeutic act should be capable of assuming total responsibility for the care of these patients. An outgrowth of the association of a member of the Department of Medicine with the Department of Radiotherapy has been an awareness of the need for well trained radiotherapists who are sufficiently clinically oriented to be capable of and willing to assume full responsibility for the management of their patients. Even more important, they must be able to recognize when assistance is necessary and be able to initiate consultations with their colleagues in other disciplines.

Equally, it has become apparent that it is necessary to have well trained internists

who are sufficiently oriented in the clinical and biologic response to ionizing radiation so that they may assist the radiotherapist in the management of such patients. The internist must be prepared to seek out that which is radiation induced and that which occurs in a population of cancer patients of this age group who are referred for radiotherapy. In this manner the maximum number of patients will have an opportunity to receive a therapeutic course of ionizing radiation.

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HEMIPELVECTOMY IN THE TREATMENT OF ADVANCED CANCER*

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IN SPITE of the recent trend to discredit the efforts to cure cancer by more extensive surgical and radiologic procedures and the number of studies which attempt to show that the early treatment of cancer is not attended by any great improvement in cure rates, it should be obvious that un-eradicated cancer inevitably leads to death. Even inadequate treatment, whether surgical or radiologic, can be shown to cure the cases in which the cancer is limited to a single focus. The patients with more advanced tumors, however, can be cured only by a more radical approach.

The cases with occult distant metastases are never cured by either the classic approaches or extended surgical or radiologic attack. Inadequate treatment, whether surgical or radiologic, will result in some cures; *e.g.*, simple mastectomy and irradiation of the regional lymph nodes will cure any patient whose tumor is limited to the breast, and an occasional patient, in whom the carcinoma may be radiosensitive, will have the lymph node involvement controlled. Similarly, a poor radical mastectomy will accomplish the same result, since the breast is removed as well as a few of the easily accessible lymph nodes.

The classic surgical procedures for the treatment of cancer are by no means as standardized as one might believe. In a practice limited to the treatment of cancer, one often sees patients who have been reported to have had radical mastectomies or axillary dissections but which obviously have not been properly performed. The same is true of gastric resections or dissections of lymph node-bearing areas.

In spite of recent urgings to simplify the treatment of cancer by comparing the results obtained by radiotherapy with those

obtained by inadequate surgery, efforts continue to be made toward extending radical operations in the treatment of this disease. These extended operations differ from the classic cancer operations in that they attempt to better circumscribe the disease process by removing contiguous viscera or adjacent anatomic structures which might be involved. The addition of the internal mammary lymph node dissection to the classic radical mastectomy, or of a supraclavicular lymph node dissection or the anterior mediastinal lymph node dissection are such operations. The so-called "commando operation" for the treatment of intraoral cancer, the pelvic exenteration for cancer of the cervix or rectum, the upper abdominal evisceration for cancer of the stomach or pancreas, and the radical amputations for the removal of soft part sarcomas or tumors which have extended beyond the normal lymph node-bearing areas are all efforts to increase the cure rates by eradication of more advanced tumors.

The colloquium on the causes of failure in the treatment of cancer of the oral cavity, presented at the meeting of the American Radium Society in April, 1959, indicated that small cancers of the oral cavity could be treated and cured by almost any method, whether it be radiologic or surgical. The cause of failure lay in the inability to control the metastatic disease in the neck. In general, this applies to cancer in most of its forms, whether it be of the head and neck, breast, abdominal cavity, or extremities. The meticulous care with which the surgical operation is carried out determines whether or not the end result will be successful if the disease is still limited to the lymph node-bearing area. Improvement in survival rates will certainly not be accom-

* Presented at the Forty-third Annual Meeting of the American Radium Society, Colorado Springs, Colorado, May 11-13, 1961.

plished by returning to simpler and less extensive operations, once cancer has ceased to be a local process. The properly performed classic operations require skillful execution and mature judgment in the selection of patients. The extended radical operation requires even more care and judgment. While none of these procedures can be expected to increase greatly the percentage of survivals, to the individuals who are salvaged, the increase is 100 per cent.

Even the advocates of simpler methods will admit that the reason for failure of these less radical procedures is the inability to destroy completely the cancer in the local field. Since the patient with occult or distant metastases at the time of first treatment is seldom cured, it is only by complete eradication of cancer in the local field that cure rates can be improved. While, in mammary cancer, occult metastases are frequently present at the time of primary treatment, a persistence of local disease after inadequate therapy does not diminish the chance of the development of distant metastases. Head and neck cancer has a great tendency to remain localized to the tissues above the clavicles. In patients dying of cancer of the cervix, 50 per cent have their disease limited to the pelvis; extended efforts might salvage some of these cases.

The extended surgical procedures all require considerable psychic adjustment, both on the part of the patient and the patient's family. The mutilations resulting from the commando operation, the problems of the diverted urinary and fecal streams in the pelvic exenteration, and the added mutilation of the internal mammary lymph node dissection have all been accepted by both patients and physicians. Hemipelvectomy as a method of increasing the cure rate or for palliation of cancer in the pelvis or lower extremity also requires considerable adjustment and effort on the part of the patient for rehabilitation. No person willingly accepts mutilation or deformity, but there are few people who will

TABLE I
HEMIPELVECTOMY PATIENTS

Histologic Type	No. of Cases
Malignant Melanoma	13
Rhabdomyosarcoma	5
Neurogenic Sarcoma	3
Fibrosarcoma	4
Synovial Sarcoma	2
Liposarcoma	2
Dermatofibrosarcoma	1
Osteogenic Sarcoma	1
Chondrosarcoma	1
Squamous Carcinoma	5
	37

not accept these as the price they must pay for possible continuation of life.

In a personal experience with 37 patients (Table I) treated with hemipelvectomy, there has been no operative death. Most of these patients succeeded in wearing a prosthesis and have returned to their previous activities. Figures 1 to 6 show the results obtained in some of the cases. Thirteen of the cases were operated for malignant melanoma. Unfortunately, all of these were advanced cases with satellitosis and/or large fungating tumors. Three succumbed to distant metastases in less than one year; 3 lived one to two years and died of distant metastases; 3 lived two to three years and died of metastatic disease; 1 survived over five years, then died of pulmonary metastases; and 3 are living at the present time. Of these three, one has cerebral metastases, another has a solitary pulmonary metastasis and has refused surgical removal, and one is living without evidence of disease at twelve months. Obviously, hemipelvectomy has added little to the cure rate of advanced melanoma, but the removal of a foul, edematous, painful, ulcerating extremity must be considered worthwhile palliation.

Of 5 patients with myogenic sarcoma in this series, 2 are living and well after eleven years and eight years, respectively; another lived four years and six months, returned to

FIG. 2. Patient shown in Figure 1 after hemipelvectomy, wearing an artificial limb. He returned to his job as sheriff in a small southern community.

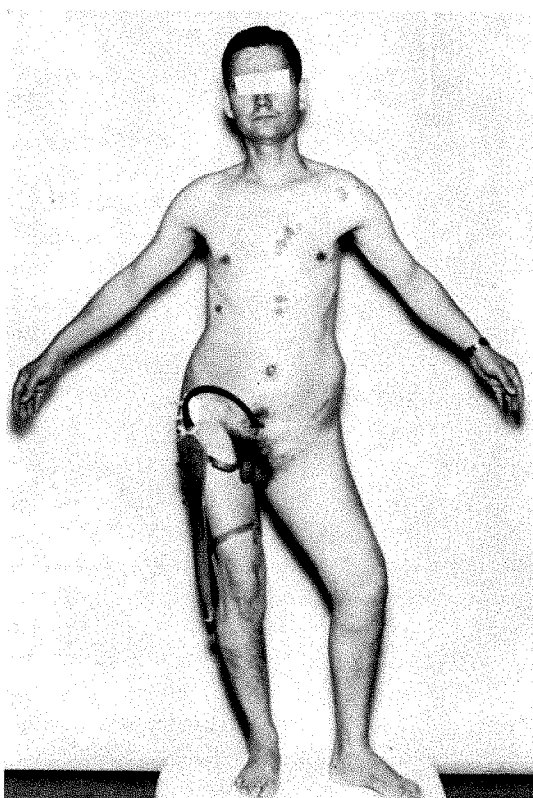
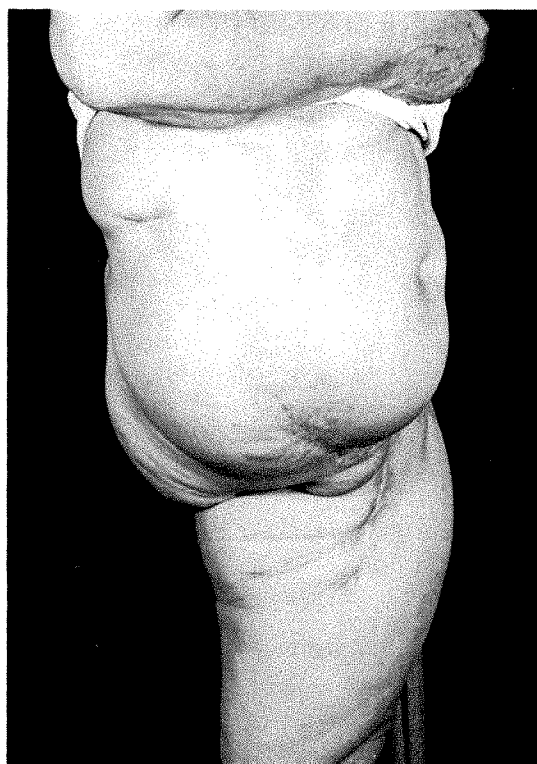
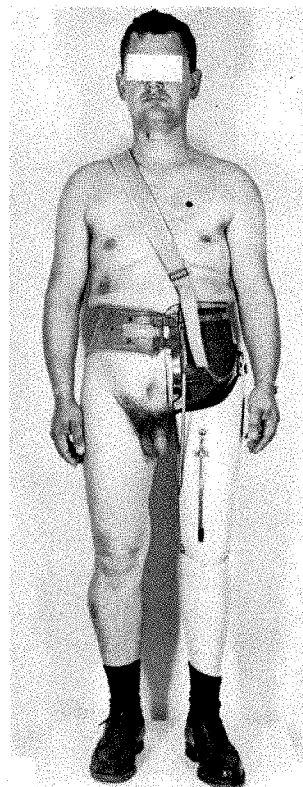


FIG. 1. This patient had Ollier's disease and a large chondrosarcoma which developed in a benign chondroma of the left ilium. The tumor was so large that it obstructed the urethra and required suprapubic cystotomy. The patient was bedridden. Many other chondromas, as well as psoriasis, were also noted.



FIG. 3. Side view of a patient who had had a hemipelvectomy for uncontrolled vulvar cancer with metastases in the groin.



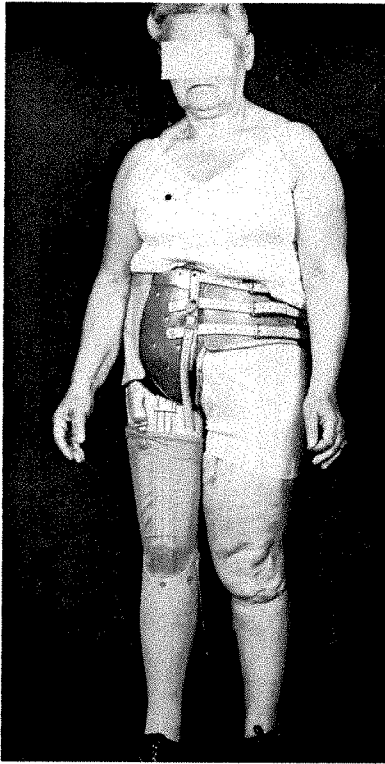


FIG. 4. Patient shown in Figure 3 wearing an artificial limb. She is living and free of disease six years after the hemipelvectomy, and has been managing her household and taking care of her family.

his job and supported his family during the greater part of that time before dying of pulmonary metastases. None of the 3 neurogenic sarcoma cases survived over eighteen months. Three of the patients with fibrosarcoma are living and well eight, four, and three years, respectively. Of the liposarcoma patients one is living and well three years. The only case of dermatofibrosarcoma succumbed to local recurrence and distant metastases after multiple amputations which led to hemipelvectomy. The only case of osteogenic sarcoma died at fourteen months of pulmonary metastasis. The single patient with chondrosarcoma in this group presented with an advanced sarcoma and Ollier's disease. He was able to return to his job as sheriff and lived six years and eight months. Both cases of synovial sarcoma succumbed promptly to distant metastasis.

Of the 5 squamous cell carcinoma cases, 2 were in patients with chronic osteomyelitis of many years' duration. Both patients were dead in six months and one year, respectively. Another patient with an advanced squamous cell carcinoma of the vulva with involvement of the inguinal lymph nodes and iliac vessels is living and well six years, with no evidence of disease. One patient with epidermoid carcinoma of the skin and wide dissemination throughout the extremity, after the simultaneous ligation and stripping of varicose veins and excision of the squamous cell cancer, has lived eight and one-half years. The last patient who had an *in situ* carcinoma of the cervix treated by radiation developed a solitary metastasis in the left ilium with fracture. Hemipelvectomy was done to rid the patient of a painful extremity. She lived nine months before death resulted from renal sepsis.



FIG. 5. Side view of a patient after hemipelvectomy for extensive recurrent rhabdomyosarcoma of right upper thigh.

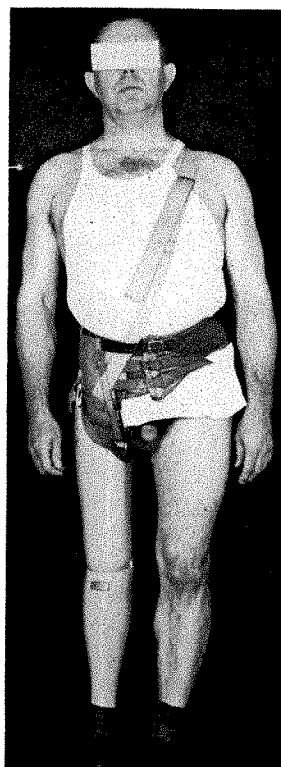


FIG. 6. Patient shown in Figure 5 wearing an artificial limb. This patient is alive eleven years since the removal of the tumor by hemipelvectomy and continues to earn his living as an electrical engineer.

CONCLUSIONS

1. Hemipelvectomy is a safe procedure. In 103 patients on whom it was performed at the Mixed Tumor Service of Memorial Hospital, no operative deaths occurred. This series includes 37 personal cases.

2. While indications for hemipelvectomy have been considered few, it is our opinion that the operation should be more widely practiced in such diseases as high-lying soft part sarcomas of the lower extremity and in

cases of carcinoma involving the pelvic organs and genitalia. It might yield a satisfactory salvage in malignant melanoma if performed early in the course of the disease.

3. While extended radical operations will not greatly alter the over-all cure rates of cancer, personal experience with 37 cases yielded a five year survival rate of 18.9 per cent, or a five year cure rate of 20.8 per cent if the 13 cases of advanced melanoma are not included in the series.

4. The fact that palliation, comfort, and sometimes cure in advanced cancer can be obtained justifies this radical but safe surgical procedure.

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EFFECTS OF THE COMBINED ACTION OF ROENTGEN RAYS AND A CHEMICAL CARCINOGEN (DAB) ON THE RAT'S LIVER*

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AT THE present time, there is an abundant literature concerning the effects of ionizing radiation and of certain azo dye carcinogens on the hepatic cells. However, there have been few studies on the combined action of these two agents. Even where the combination of the two has been studied, the results are confusing and difficult to interpret because whole body irradiation was used. Actually, one of the investigators³ concludes that irradiation retards the formations of hepatoma, while two others^{5,12} feel that it increases the incidence.

We report here the first results of our work in which only a part of the rat's liver was irradiated, following which the animals received a steady diet of *p*-dimethylaminoazobenzene (DAB), better known as butter yellow, mixed with their feed.

MATERIAL AND METHOD

Adult, mostly male, Wistar rats raised on a complete laboratory formula and weighing about 420 g. were used. For this particular series of experiments, 59 rats were employed. In a group of 24, using a single large dose of roentgen rays, about one half of the liver was irradiated, the unirradiated portion serving as a control. The remaining 35 animals, following irradiation and a one month waiting period, were started on a dietary regimen deficient in protein and riboflavin* and containing 0.6 g./kg. of DAB. This is reported in detail in previous publications.¹⁻⁶

* The ingredients were pure starch of rice 7,900 g.; casein 1,200 g.; pure corn oil 2,000 g.; salt mixture 400 g.; vitamin B₁ 0.01 g.; vitamin B₂ 0.02 g.; vitamin B₃ 0.025 g.; calcium pantothenate 0.06 g.; choline chloride 0.3 g.; potassium iodide 0.021 g.

Three different fields of irradiation were employed (Table 1):

1. In a group of 36 rats, a ventral, triangular field was drawn on the anesthetized (rectanol) animals held supine on a small board. One leg of the triangle followed the oblique edge of the right costal margin; the external leg followed the right lateral edge of the body; the anterior leg was perpendicular to a line joining the median line at a point 3-4 mm. above the xyphoid (Fig. 1). Utilizing such a field, the entire right lobe

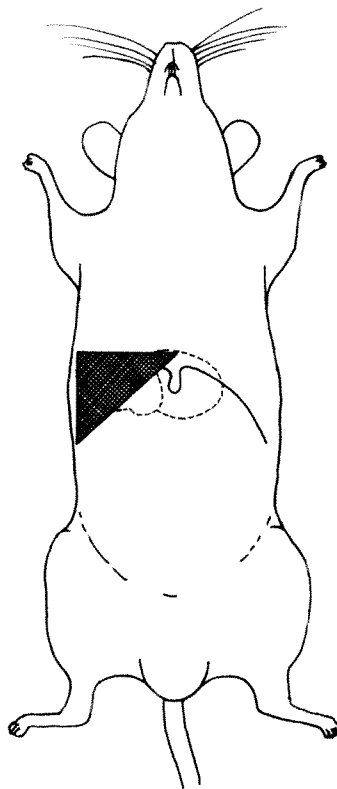


FIG. 1. Sketch showing triangular field used for a group of 36 rats.

* Presented at the Forty-third Annual Meeting of the American Radium Society, Colorado Springs, Colorado, May 11-13, 1961.

TABLE I

Radiation Only			Radiation and DAB		
Right Part of Liver					
Doses in r	No. Rats	Survival in days	No. rats	Survival after Radiation	Survival after • • DAB
500	5	1-75-140-164-217	5	87-163-183-230-235	60-146-166-172-177
1,500	5	111-186-215-255-277	14	53-58-59-62-63-73-87-94- 127-143-147-178-180- 250	18-24-27-33-37-38-55-63- 92-113-114-143-165-220
3,000	4	26-41-42-47	3	150-160-233	99-117-182
Entire Liver					
3,000	2	19-116	3	45-63-147	19-37-121
Exteriorized Lobes of Left Part of Liver					
3,000	8	(4<1)-2-29-36-46	10	36-57-60-69-77-80 90-102-111-146	1-21-23-24-40-43 46-64-67-101

and about one half of the bifid, middle lobe were irradiated. The remaining liver and body parts were protected by sheets of lead.

2. In 5 rats only, the entire liver was irradiated.

3. In 18 animals, we employed a technique derived from that of Weinbren *et al.*¹¹ This consisted of directly irradiating the two large anterior lobes of the liver (the left and the bifid) exteriorized at laparotomy, the remaining lobes and other parts of the animal being protected (Fig. 2).

In all cases, the radiation factors were identical: 250 kv.; 12 ma.; filtration 0.3 mm. Cu+2 mm. Al; target-skin-distance 29 cm.; and an output of 200 r/min. The

doses administered to the skin were 500 r in 10 animals, 1,500 r in 24 animals and 3,000 r in 7 animals. Of the animals with exteriorized livers, 17 received 3,000 r and a single animal received 4,200 r.

RESULTS

We will report successively: (1) the results relative to the action of the increasing doses of roentgen rays; and (2) the results of the action of combined ionizing radiation and chemical carcinogen (DAB) on the hepatic parenchyma.

A. EFFECT OF IONIZING RADIATION ON THE LIVER

Before considering our findings in which a part of the liver was exposed to 500, 1,500

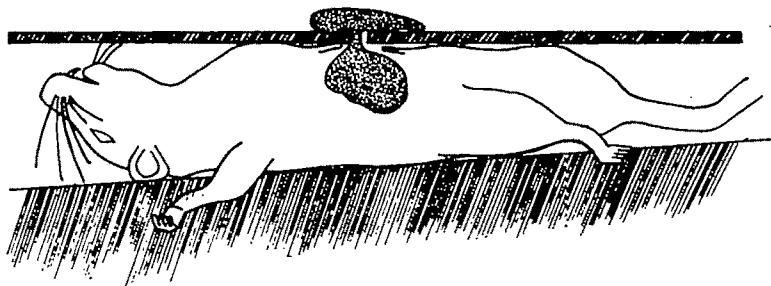


FIG. 2. Sketch showing the technique derived from that of Weinbren *et al.*¹¹ in which two large anterior lobes of the exteriorized liver are irradiated.

and 3,000 r respectively, we will review the more or less comparable experiences of others; however, it is impossible to enumerate the articles which describe hepatic morphologic and functional modifications following whole body irradiation. We can generalize the findings to the situations: (a) where sublethal doses were administered with resulting prolonged survival. The quantity of radiation received by the hepatic cells was small and the reversible changes that were seen were principally the increase of glycogen, followed by overloading with lipid. It is well known, however, that these same changes occur even when the liver is protected during the course of irradiation of the rest of the body; and (b) where high doses were used so that death ensued so rapidly that cell changes did not have time to appear.

From the few published works on the irradiation of only the liver of the rat, we can draw the following conclusions: the early manifestations (of cell edema followed by atrophy, and fatty infiltration) are transient. Similarly, with 2,500 r, the hepatic tissue appears to be restored after thirteen days.⁸ A dose of 1,000 r produces changes in mitochondrial structure and diminishes the activity of certain enzyme systems, particularly those concerned with oxydative phosphorylation;¹⁰ however, a dose of 20,000 r does not prevent repair from occurring.²

During the past few years, the effects of roentgen rays on the regeneration of the rat's liver after partial hepatectomy have been extensively studied. Notably, one can show that irradiation just before or several hours after surgery produces a delay in the synthesis of DNA as well as in the appearance of mitosis.⁴ Recently, it was noted again that even a year following the irradiation of both exteriorized liver lobes with a dose of 5,000 r, the apparent morphologic changes were very slight; however, a partial hepatectomy produced in the irradiated lobes a large number of abnormal mitoses.¹¹ Again this demonstrated that the classic phenomenon of latent radiolesions

persists indefinitely in this radioresistant organ.

Our own experiments in which a part of the liver was irradiated demonstrated the following findings.

(1) *Dose of 500 r.* These first experiments confirmed the radioresistance of the hepatic cells. After a survival of 1, 75, 140, 164 and 217 days, the macroscopic examination at autopsy demonstrated no gross difference between the irradiated and the nonirradiated zones, both areas having a normal appearance. Samples were prepared and stained with hematoxylin and eosin. Histologically, except for an impression of a slight increase in the number of binucleate cells in the irradiated part (precise cell counts were not done), there was no difference noted between the two areas.

(2) *Dose of 1,500 r.* The animals were followed for 111, 186, 215, 255 and 277 days. Four of the rats manifested no general damage, or deterioration. Their weight at the time of sacrifice was superior to that at irradiation. However, 2 animals demonstrated a distinct atrophy of the bifid and right lobes. This was compensated for by an appreciable hypertrophy of the left lobe. In all cases, the normal ratio of the total body weight to the total liver weight was re-established. Again, histologic examination of the hepatic cells demonstrated nothing that would identify the irradiated portion, except (as noted above) the impression of an increase in the number of binucleate cells and of large nuclei. Again, these were not documented by precise cell counts. In 2 cases, we noted a swelling of the perivascular connective tissue of the portal spaces.

(3) *Dose of 3,000 r.* This dose was not well tolerated. There were 4 rats that succumbed 26, 41, 42 and 47 days after irradiation. However, the experiment was sufficient to demonstrate that after one month atrophy and compensatory hypertrophy were present. At this dose, the perivascular connective tissue swelling was more characteristic; yet, the hepatic cells showed no morphologic alteration.

(4) *Dose of 3,000 r to Exteriorized Lobes.* One can attribute some inconsistencies in the results to an inability to precisely localize the field of irradiation to include only a particular part of the liver. This applies to cases which were irradiated, as well as those in which the combination of irradiation and azo dye was employed. In order to correct this we used, as mentioned above, the technique recently described by Weinbren and his collaborators¹¹ of directly irradiating the particular lobes exteriorized at laparotomy. We delivered 3,000 r to either the left lobe, or, more often, to both the left and the bifid lobes. (At the present time we have a series of animals under study which have received 1,000 and 1,500 r using the above method.)

The premature mortality among the first 8 rats operated on resulted in necessary operative precautions in order to eliminate accidents as well as the formation of secondary adhesions. Under experimental conditions, the rapidity of the atrophy of the irradiated lobes and the simultaneous hypertrophy of the nonirradiated lobes are most striking. Yet, the trabecular structure of the lobules and the general aspect of the cells are conserved. The rare areas of necrosis can be considered as secondary to the alteration of the surrounding vessels which are involved in the swelling of the vascular connective tissue of the portal spaces, rather than a direct action of the roentgen rays on the hepatic cells.

B. THE COMBINED ACTION OF RADIATION AND DAB

Before considering experimental results, it is well to review first the changes in the liver of rats receiving a dietary regimen of butter yellow. In spite of frequent individual differences, it is possible to outline the following stages and progressive changes in the hepatic structure: (a) *First two weeks.* Anomalies and degeneration of scattered cells. (b) *Second two weeks.* Appearance of the process of regeneration with new formation of biliary canaliculi starting from the portal spaces. (c) *Second month.* Marked proliferation of the new canaliculi sur-

rounding the lobules, with penetration into and disruption of these lobules. (d) *Third month.* Formation of canalicular adenomas either localized or diffuse. (e) *Fourth month.* Differentiation of the parenchymal nodules of regeneration; also, malignant change may appear at this time (the earliest appearance of cancer was found on the 105th day). (f) *From the fifth to the eighth month.* Appearance of different types of multicentric carcinomas in nearly all animals on the average of about the 180th day.

The fact that the liver lobules react to chronic intoxication in various ways presents a problem. The reason for this is not understood; however, samples from different sites of the liver show an uneven distribution of the changes of fatty infiltration, fibrosis, cholangiectasis, inflammatory reaction, etc. Also, each liver lobule acts as an independent unit insofar as progression of the precancerous lesions is concerned. In order to elucidate this, serial sections of the entire organ will have to be studied. Our results are based on examination of two or three random biopsies taken from the irradiated and nonirradiated parts of the liver.

(1) *Dose of 500 r.* Five animals were sacrificed or died spontaneously 87, 163, 183, 230 and 235 days after irradiation; they had received a daily ingestion of azo dye in their feed during the previous 60, 146, 166, 172 and 177 days, respectively. Autopsy findings showed that the expected lesions consisted of disseminated little nodules which were scattered over the entire surface of the organ, but, in certain animals, and notably in the 2 that survived the longest, several of these nodules were quite large and vegetating. They were located in the nonirradiated left lobe.

The histologic examination confirmed, in general, a retardation of the evolutive stages in the irradiated lobes. In particular, proliferation of the bile canaliculi was markedly reduced. The parenchymal regeneration was frequently found to be retarded. Malignant transformation existed in the nonirradiated lobe in those rats

which had received the DAB 146, 172 and 177 days, respectively. A single, beginning hepatoma was found in one of the specimens from an irradiated portion of the liver in the rat on the diet for a period of 172 days.

(2) *Dose of 1,500 r.* In this group 14 animals survived 53, 58, 59, 62, 63, 73, 87, 94, 127, 143, 147, 178, 180 and 250 days after irradiation, having been maintained on the regimen of DAB during the previous 18, 24, 27, 33, 37, 38, 55, 63, 92, 112, 114, 143, 165 and 220 days. This series followed the progressive alterations under the double influence on the irradiated side compared to the single influence of the azo-dye on the protected side. The findings confirmed in general those that had been shown in the rats receiving 500 r, although several aberrant cases were noted.

We found no gross differences between the irradiated and nonirradiated portions of the liver in the animals sacrificed during the first month of the chronic dietary regimen. The only histologic finding in the irradiated part was the inhibition, more or less marked, of the growth ability of the new canaliculi. After the first month, the marked atrophy of the right lobe and less frequently of the bifid lobe was noted. This corresponded with hypertrophy of the unirradiated lobes.

During the second and third months, a slight retardation in the development of the lesions in the irradiated area was noted in a few animals; however, a sample from an irradiated bifid lobe of a rat sacrificed on the 147th day contained an adenoma more advanced than any found in the nonirradiated lobe. On the other hand, a sample obtained from a nonirradiated lobe of a rat sacrificed on the 178th day showed marked cirrhotic and proliferative changes which were in marked contrast to the absence of canalicular proliferation and the near normal appearance of the lobules on the irradiated portion. This was also noted in a rat sacrificed on the 180th day, where the lesions of the control (nonirradiated) lobe

contained malignant change. A rat sacrificed on the 250th day had voluminous tumors in the nonirradiated lobe, whereas the irradiated lobes showed absolutely no tendency to malignant change.

(3) *Dose of 3,000 r.* In this group there were 3 rats which were sacrificed 150, 160 and 233 days after irradiation or after being on DAB 99, 117 and 182 days, respectively. In the first of these animals a striking histologic change was seen between the cirrhotic, precancerous adenomas of the nonirradiated portion and the fatty infiltration of the irradiated side. The animal sacrificed on the 160th day presented atrophy of the right lobe, suggesting it was the only lobe irradiated, whereas the histologic lesions were distinctly more advanced in the bifid lobe, where an adenocarcinoma was present. The last animal had a large hepatoma of the left lobe; yet, one of the nodules taken from the bifid lobe also contained a hepatoma.

(4) *Dose of 3,000 r Applied to Exteriorized Lobes.* In order to eliminate the question of field localization, we employed the technique mentioned above. This series contained 10 animals which died spontaneously or were sacrificed 36, 57, 60, 69, 77, 80, 90, 102, 111 and 146 days after irradiation and had been on the DAB regimen 1, 21, 23, 24, 40, 43, 46, 64 and 101 days, respectively. None of these animals had passed the latent period required for the development of malignant change.

In all cases the atrophy of the irradiated and the parallel compensatory hypertrophy of the nonirradiated lobes were well accentuated. In the animal sacrificed 146 days after irradiation, the two halves of the liver, which initially were nearly equivalent in weight, showed a marked difference with the irradiated lobe weighing 2.52 g. and the nonirradiated lobe weighing 11.87 g. The histologic findings of the animal sacrificed after 36 days permitted one to distinguish between the two sides because of the absence of canalicular proliferation and the presence of swelling of the collagen of the

perivascular sheaths on the irradiated side. However, in the rat receiving DAB for 40 days the difference was grossly visible because of the absence of adenomas in the irradiated lobes and the presence of well developed adenomas in the nonirradiated lobe.

DISCUSSION

When undertaking these experiments, it was difficult to predict what the results would be. It appeared that either of two opposite hypotheses might be supported: (1) There could be an acceleration of the carcinomatous process by the addition of the cancerogenic properties of each of the two agents and (2) the malignant transformation under the action of DAB could be retarded because of the possible slackening of the processes of repair by the irradiation which preceded the chemically induced cancer formation.

The reported results seem to eliminate the first of these hypotheses and to support the second. This is verified by the fact that all the carcinomas, whether formed in the irradiated or nonirradiated lobes of the liver were recognized during the expected development period of between 117 and 220 days. There was no case of early development either in the lobe atrophied by irradiation or in the lobe showing compensatory hypertrophy. Thus, even while awaiting the results from experiments now underway using the technique of irradiating the exteriorized lobes, we do know that carcinomas were found somewhat more often in the nonirradiated portion of the liver.

More generally, we can say that because of irradiation there was a delay in the appearance of the destructive process and of the subsequent regeneration which the hepatic parenchyma customarily demonstrates under the influence of the azo dye. The most characteristic phenomenon was the feebleness and prolonged delay in the appearance of the new hepatic cells arising from the bile canaliculi. This was described in 1952 by Price *et al.*⁹ and was confirmed by the present experiments.

Partial irradiation of the liver has many analogies with partial hepatectomy. The extraordinary regenerative ability of hepatic tissue manifests itself here, also by compensatory hypertrophy. In the case of progressive regression of a parenchymal mass of the irradiated lobe, the hypertrophy in the other lobe reaches a level equally progressive. This permits the ratio of the total weight of the liver to the total weight of the body to remain constant. This finding was also noted in those rats on a regimen of DAB which caused a rapid loss of weight. Brisk, relative augmentation of the weight of the liver is one of the manifestations which indicates that cancerous transformation has taken place.

The experiments reported here and which were undertaken with a limited scope, however, have presented more problems than they have solved. This is true because of the wide gaps in our knowledge regarding this organ. It appears that two modes of regeneration exist in the liver: (1) The first, which has been well studied, commences immediately after partial hepatectomy and consists of a multiplication of parenchymal cells by mitosis. From previous experiments,⁶ we know that this mechanism is retarded by DAB. (2) The second type of repair manifests itself slowly in those animals in which the intoxication by DAB causes the progressive destruction of hepatic cells. It originates principally from the neoplasia of the bile canaliculi and is not modified by partial hepatectomy,⁶ but is definitely retarded by irradiation.

The damage to the hepatic cells by the two carcinogenic agents, irradiation and butter yellow, does not appear to be additive. Actually, the roentgen rays appear to exercise a slight protective effect against the azo dye. Perhaps this might be interpreted to mean that the radiation effect is predominantly on the nuclei, whereas the direct action of the DAB is predominantly on the cytoplasm.

It is possible that some variation in the application of these two agents will suggest

or explain certain pertinent points concerning the mechanism of malignant transformation.

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THE SYSTEMIC EFFECTS OF LOCALIZED RADIATION ON SERUM PROTEINS IN HUMANS*

A PRELIMINARY REPORT

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THE systemic effects of total body radiation upon animals and humans have been recorded in a voluminous literature.^{2,3,18} Much of this work has dealt with acute syndromes and lethal doses of radiation rather than more subtle physiologic effects. The effects upon the hemopoietic system have been studied intensively since the first report by Senn²² in 1903. These studies have included changes in the bone marrow, thrombocytes, white blood cells and red blood cells.^{6,10,14,20,21}

More recently, there has been great interest and research in the effects of total body radiation on immunity mechanisms, particularly with reference to tissue transplantation.⁵ The systemic effects of localized radiation have also been studied extensively with reference to lethality of dose and modification of lethality by shielding.^{2,18} Physiologic changes in the body remote from the target of radiation have not been reported with any frequency. In a comprehensive review⁷ in 1942, Dunlap stated: "It is not known how local radiation affects distant tissue." The mechanism is still unknown; however, it is felt worthwhile to report on one systemic radiobiologic effect of localized radiation: the effect of localized tumor dose radiation on the serum protein electrophoretic pattern in humans.

MATERIALS AND METHODS

Cancer patients were selected for this study at random. In some patients, radiation was applied postoperatively to the cancer bed. In others, the radiation was

applied directly to the tumor mass or to the spleen.

Serum protein electrophoretic patterns were determined for each patient prior to radiation therapy. At the estimated peak of radiation effect, electrophoretic patterns were repeated and comparisons were made in the distribution of the serum protein fractions for each serum obtained before and after radiation.

It is probably worthwhile to indicate briefly what is meant by an electrophoretic pattern. Electrophoresis is a process by which a complex protein moiety is fractionated by running an electric current through it. The filter paper method developed in 1950 by Tiselius, Cremer and others is a simple technique which gives reproducible results. In this method, a small quantity of serum is applied to a strip of filter paper moistened with veronal buffer. As an electric current passes through the paper, the serum protein components move away from the point of application with the lightest protein, albumin, moving the fastest. The protein fractions identified by this technique are albumin, and the globulins alpha, beta and gamma. Gamma, being the heaviest, moves the least from the point of application. The strip is then heated to coagulate the protein and stained. The quantity of each protein fraction is determined by the amount of stain deposited and is measured electronically.

Fractionation in this study was performed by using the Spinco-Durran apparatus and quantitated by a companion analytical method.

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TABLE I
THE SYSTEMIC EFFECTS OF LOCALIZED RADIATION ON SERUM PROTEINS IN HUMANS

Disease Treated	Tissue Dose	Fields	Results				
			Albumin	Alpha I	Alpha II	Beta	Gamma Globulin
Breast Carcinoma Postoperatively	4,400 r	100 cm. ²	41.6	4.3	21.5	10.0	22.5
		150 cm. ²	33.6	5.9	13.6	16.5	30.0
Breast Carcinoma Postoperatively	4,400 r	100 cm. ²	43.5	5.6	8.5	19.8	22.5
		150 cm. ²	44.2	4.5	4.5	18.0	28.2
Breast Carcinoma Radiation Only	4,400 r	100 cm. ²	51.0	3.2	9.7	19.5	16.7
		150 cm. ²	52.0	4.1	13.0	12.5	18.3
Breast Carcinoma Postoperatively	4,400 r	100 cm. ²	49.0	4.8	12.6	10.5	23.1
		150 cm. ²	44.4	5.6	16.7	11.2	22.2
Breast Carcinoma Radiation Only	4,400 r	100 cm. ²	45.8	8.5	14.2	14.2	17.1
		150 cm. ²	48.0	4.8	14.5	12.9	19.8
Kidney Cancer Postoperatively	2,000 r	150 cm. ²	53.0	6.0	13.0	12.0	17.0
			33.5	4.6	20.3	20.3	23.0
Hodgkin's Disease Neck	2,000 r (skin)	200 cm. ²	52.5	3.6	16.3	13.6	13.6
			59.2	3.8	8.7	11.4	16.5
Leukemia Spleen	1,500 r (skin)	100 cm. ²	44.0	6.5	9.8	18.3	21.5
			40.7	5.5	10.4	17.0	26.3
Ovary	2,500 r	150 cm. ²	42.3	6.9	13.8	13.8	23.7
			45.9	7.2	13.2	8.1	25.5
Astrocytoma	2,500 r(50%)	100 cm. ²	55.5	5.5	12.7	11.8	14.5
			55.0	9.4	11.7	11.8	17.6
Xanthoma (H.S.C.)	2,000 r	100 cm. ²	55.2	2.6	11.0	12.5	16.4
			52.8	6.5	11.3	12.2	17.5
Normal Values	—	—	60-70%	2-5%	5-10%	8-12%	10-15%

TOTAL BODY RADIATION

The depressive effects of total radiation on the hemopoietic system are well known.^{7,10,20,21} There is a general decrease in cellularity with the exception of the plasma and reticulum cells which may appear relatively increased. There is also some evidence of an absolute increase, a proliferation of plasma cells.¹³ Some investigators feel that plasma cells are a major source of gamma globulin.^{9,19}

Eleven cases were irradiated with tissue

doses ranging from 2,000 r to 4,400 r. Changes were noted in all of the protein fractions, but, with the exception of those in gamma globulin, no definite pattern for the changes was established.

The gamma globulin was increased in 10 of the 11 cases. The increase was minimal to moderate and ranged from 1 to 8 per cent (Table I.) One might assume that this protein fraction would remain unchanged or even increase; however, it is well known that total body radiation can ablate the

immunity mechanisms causing a reduction in plasma cells and gamma globulin.⁵ This point remains to be clarified.

LOCALIZED RADIATION

As previously stated the effects of localized radiation on the white blood cell count have been known since 1903.²² In a summary of the subject by Goodfellow¹⁰ in 1936, both direct and indirect effects of radiation on the white blood cells were considered and a leukotoxin was postulated. Radiation of the spleen in chronic granulocytic leukemia may cause an alteration of the bone marrow with a drop in the white blood cell count.¹⁶ Since this occurs in the absence of significant direct radiation to the marrow, it is considered a remote or indirect effect.

DISCUSSION

It has been shown that the serum of rabbits is altered twenty-four hours after a single large dose of whole body radiation was delivered.¹⁵ The serum at that time contains a physically characterized factor not found in controls which inhibit cell division and bacterial growth. This effect is not present when the serum is irradiated *in vitro*. It is not unreasonable to assume that irradiation of large blocks of tissue rather than of the total body might cause a similar alteration or humoral change in the serum. Changes in nuclei acid synthesis outside the field of radiation which have been reported¹² might well be due to the effects of a humoral factor on cell division.

Although indirect effects of local radiation have been established, the mechanism of this process has not, as yet, been determined. The possibilities are: (1) a breakdown product of the irradiated tissue acting as a humoral agent; (2) release of a hormone triggered by the radiation; and (3) a neurogenic reflex triggered by the radiation.

Regardless of the mechanism at work, this preliminary study would seem to indicate that there may be a plasma cellular response to localized radiation as reflected

in the consistent moderate increase in gamma globulin levels.^{9,22} Plasma cells are probably a component of the reticuloendothelial system although this depends on definition.²⁴ As part of this system, they may respond to innumerable stimuli—chemical, physical, bacterial, nutritional, etc.^{23,24} The response of the reticuloendothelial system to total body irradiation has been variable with inhibition of humoral antibody formation as well as failure of alteration of phagocytosis.⁸ It is not unreasonable, therefore, to assume that localized radiation may through one of the mechanisms suggested above cause stimulation of the reticuloendothelial system, plasma cell hyperplasia or hyperfunction and increased gamma globulin formation.

SUMMARY

Serum electrophoretic patterns were recorded before and after irradiation of large local blocks of tissue in humans. Of 11 cases, 10 showed a slight to moderate increase in gamma globulin with no consistent change in the other protein fractions.

It is suggested that this gamma globulin change represents a stimulation of the plasma cell component of the reticuloendothelial system. This stimulation is most likely a remote effect of the radiation.

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POSTIRRADIATION TREATMENT OF LETHAL TOTAL BODY IRRADIATION BY CELL-FREE SPLEEN EXTRACTS*

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THE treatment of every disease is based on two fundamental approaches: the curative and the preventive or prophylactic. These classic approaches apply also to the treatment of lethal total body irradiation. We shall consider the prophylactic approach to lethal total body irradiation in accordance with the age old maxim of medicine that prophylaxis is better than cure.

With regard to the prophylaxis of lethality in total body irradiation, there are two general methods available, namely pre-irradiation and postirradiation treatment. A review of the literature¹⁷ shows that the majority of investigators has selected the prophylactic approach by administering chemicals prior to irradiation. For this type of treatment the term "chemical protection" was suggested by Latarjet and Gray.¹⁵

"Chemical protection," *i.e.*, pre-irradiation treatment of the lethal effect of total body irradiation with chemicals, is beset with numerous difficulties.¹⁶ The most significant of these are:

1. Chemicals to be used in this manner must be available at the time of irradiation in a sufficient concentration to counteract toxic substances formed during the impact of irradiation. Experience has shown that in such concentrations suitable chemicals are quite toxic and that some may even cause death. When given after irradiation, most chemicals fail to reduce mortality.¹⁶

2. The protective effect of such chemicals is very short lived. This makes it necessary to administer these chemicals from a few minutes to a few hours prior to irradiation.

Such exact timing between administration of these chemical compounds and exposure to irradiation is, however, in most instances impossible under conditions prevailing in industrial as well as in military medicine.

3. In addition, in most instances administration of these chemicals necessitates the intravenous route for their effectiveness. This constitutes a formidable logistics problem if and when the prophylactic treatment of larger numbers of persons must be accomplished.

4. Pre-irradiation application of chemicals entails the risk of reducing tumor radiosensitivity to the same extent as this treatment increases the radioresistance of the tumor host, a problem of particular interest to the radiation therapist.

5. Even if scientific ingenuity were to produce a substance as harmless as aspirin, which could be taken by mouth and which would protect a human being for 24 hours, there would still remain some serious obstacles. For on the basis of pharmacologic experience it appears highly probable that persons engaged in work entailing a radiation hazard and to whom such drugs would be administered five times weekly over the entire period of their gainful employment would suffer from chronic intoxication.

These disadvantages show that the so-called "chemical protection" offers but little probability of providing an effective and practical method for the prophylactic treatment of lethal total body irradiation.

Although pre-irradiation treatment with chemicals as a prophylactic method of combating radiation mortality does not appear

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as a hopeful approach, this does not mean that a prophylactic treatment of lethal total body irradiation is precluded. Fortunately, the other approach to the problem, *i.e.*, postirradiation treatment offers definite chances for successful therapy.

From the standpoint of prophylaxis it must be considered as fortunate that the acute radiation syndrome leading to death shares with infectious diseases the incubation (latent) period between exposure and the onset of symptoms. It appeared, therefore, promising to institute therapeutic measures during this period which might ameliorate or completely suppress the subsequent course of the disease, as this has been done successfully in infectious diseases. Such prophylactic treatment is also more advantageous from the point of view of civilian as well as military medicine. Obviously postirradiation prophylaxis can readily avoid many of the drawbacks of pre-irradiation prophylaxis with chemicals. Pertinent investigations were, therefore, initiated.

We selected cell-free spleen extracts for postirradiation treatment of lethal total body irradiation on the basis of our observation that in various animal species, regardless of the condition of the bone marrow, a certain percentage of animals recovered from the impact of irradiation provided that the radiation dose permitted some remnants of malpighian bodies of spleen to remain.¹ We concluded that possibly a humoral factor elaborated by the spleen might be responsible for this recovery of the bone marrow from the impact of irradiation. This hypothesis received support in experiments carried out by Jacobson,¹⁴ in which the exteriorized spleen of mice was shielded with lead during irradiation and implantation of baby mouse spleens took place after irradiation. Both procedures resulted in increased survival of the irradiated animals. Thus, we hoped to prove the existence of a humoral spleen factor, which might reduce radiation mortality through speed up of the natural recovery processes from the impact of irradiation.

METHODS

A. EXTRACTION METHOD

By trial and error¹² we succeeded in developing a standard procedure for spleen extracts to be used in studies of the effect of such extracts on lethal total body irradiation. Our methodical approach has been described in detail.² Briefly, it is as follows: Spleens are removed from the donor animals as soon as possible after killing and immediately frozen on dry ice. The organs of larger animals are cut into small pieces in order to accelerate the freezing process. The frozen spleens are then ground to a fine powder in a porcelain mortar with a porcelain pestle and cooled with dry ice. The powder is extracted for about 24 hours at refrigerator temperature with a given amount of a 0.9 per cent NaCl solution. Thereafter removal of particulate matter takes place by centrifugation at -4 to -6° C. at 4,500 rpm for 30 minutes. The supernatant fluid is first filtered through a Buchner filter under light vacuum and then through a Silas filter of 0.3 porosity under heavy vacuum. The filtrate is tested for absence of bacterial contamination and cell debris. Its volume is determined for figuring the amount of spleen extracted per ml. (so-called spleen equivalent). The entire filtrate is lyophilized in volumes of 25 to 50 ml. The vials are stored in a refrigerator for later use. Since it was ascertained that in the lyophilized state extracts could be stored for a period of about one year without a notable loss of radiation protective effect,³ lyophilized extracts were used at varying time intervals but within one year from the time of their preparation. For the study of the protective effect, the lyophilized material is reconstituted with varying amounts of distilled water.²

B. INJECTION PROCEDURE

For the evaluation of radiation protective power of extracts, one group of either mice or guinea pigs, all of male sex and of specified weight, received as small as possible a volume of highly concentrated extracts. Intramuscular injections were selected for practical reasons and started on

the day of irradiation $\frac{1}{2}$ to 2 hours after exposure; they were continued for 5 consecutive days. Another group of animals of equal numbers and the same specifications, irradiated simultaneously with the first one, received a volume of physiologic 0.9 per cent NaCl solution corresponding to that of the spleen extracts for the same period of time and served as controls.

C. IRRADIATION AND EVALUATION PROCEDURE

In our first studies 250 kvp. roentgen rays and mice exposed to various radiation doses were used. In the subsequent systematic investigations, guinea pigs served as experimental animals and were exposed to a 2,400 curie Co^{60} radiation source using a 4 pi geometry as previously described.⁴ This irradiation procedure permitted the simultaneous exposure of a larger number of animals. The use of guinea pigs appeared preferable since they show a more homogeneous response to a given radiation dose in smaller numbers than mice do. Only one standard radiation dose was employed, 650 r in air, which is approximately the $\text{LD}_{75/20}$, as established in previous studies.⁴ Termination of the observations on the twentieth postirradiation day was elected as a matter of economy and because it was found that only insignificant changes in mortality occurred after this date up to the usual termination point of 28 days.⁵

RESULTS

A. QUALITATIVE DEMONSTRATION OF RADIATION PROTECTIVE EFFECT OF CELL-FREE SPLEEN EXTRACTS

In the first exploratory study using mouse spleen extracts prepared in various ways on mice exposed to the $\text{LD}_{80/20}$ days of 250 kvp. roentgen rays, a larger number of survivors was found in the spleen treated groups when compared with their respective saline controls. While the difference in survivors for each of the individual groups was not statistically significant because of too small numbers, the total experience, however, showed 23 survivors out of 144 animals in the saline treated group and 39 survivors out of 144 animals in the spleen

treated group. This difference proved to be statistically significant ($X^2=4.6246$ and $P=0.02$ to 0.05).⁶ Thus the existence of a protective factor in cell-free saline mouse spleen extracts was demonstrated in a general way.

The question arose, whether a reduction of radiation mortality could be accomplished only with *homologous spleen extract* treatment (*i.e.*, in instances where the donor animals from whose spleens the extracts were made and the recipients were of the same animal species) or whether an *heterologous spleen extract* treatment (*i.e.*, treatment with an extract from spleens of donor species different from that of the recipient) would also be successful. An exploratory study proved the effectiveness also of heterologous spleen extract treatment.⁷ This observation encouraged further systematic studies with homologous and heterologous spleen extracts. Pertinent data are listed in Table 1.

The evidence as seen in Table 1 indicates that regardless of the nature of cell-free spleen extracts, statistically a highly significant reduction of radiation mortality ($P<0.001$) can be accomplished within the 20 days observation period. This points strongly to a common active principle in the extracts from the spleens of different species, capable of reducing radiation mortality.

B. LONG-RANGE ASPECTS OF SPLEEN EXTRACT TREATMENT

While reduction of mortality has been established beyond doubt for short-range experiments, it became necessary to ascertain whether spleen extract treatment may not produce late effects. Pertinent experiments extending the observation to approximately three months⁸ indicated that this was not the case. Animals treated with spleen extract continued to gain weight and retained this weight gain until death.⁹ Furthermore, the median survival time for these animals and for their respective controls during the second postirradiation year was about the same.⁹ This proved that spleen extract treatment *per se* did

TABLE I

SUMMARY OF RESULTS CONCERNING REDUCTION OF RADIATION MORTALITY BY VARIOUS SPLEEN EXTRACTS
IN GUINEA PIGS EXPOSED TO 650 R IN AIR OF Co⁶⁰ GAMMA RADIATION (4 PI)

Experiment	Recipient Species	Donor Species	No. of survivors on the 20th day		X ²	P
			Saline Controls	Extract Treated Animals		
I	Guinea Pig	Guinea Pig	11/40	28/40	14.459	< .001
II	Guinea Pig	Mouse	7/50	27/50	17.825	< .001
III	Guinea Pig	Dog	11/40	23/40	7.366	.01 > P > .001
Total Experiment			29/130	78/130	38.132	< .001

not shorten the life span of irradiated animals.

Autopsy findings in survivors of irradiation which died during the second post-

irradiation year or later showed that both control and spleen extract treated animals died primarily from changes produced in the kidneys. The most extreme changes noted in an animal which had served as an irradiated nontreated control and came to autopsy 985 days after irradiation are shown in Figure 1. At this time it is not possible to state definitely whether these changes occurred as a result of natural or radiation induced aging. Pertinent studies to obtain basic information on nonirradiated guinea pigs of similar age are in progress.

C. ACTION MECHANISM OF SPLEEN EXTRACTS

From the course of radiation mortality in animals treated with spleen extract and their respective saline treated controls, it was concluded that the reduction of radiation mortality might be due to acceleration of the natural recovery processes. This conclusion was based on the observation that a notable difference in the course of radiation mortality in the experimental groups and their respective saline treated controls usually did not occur prior to the beginning of the second postirradiation week. Previous studies with desoxycorticosterone¹⁰ had shown that a similar trend in the mortality curves of the hormone treated animals was attributable to a statistically significant speed-up of the recovery of the bone marrow.

In order to ascertain whether a similar mechanism is effective in animals treated

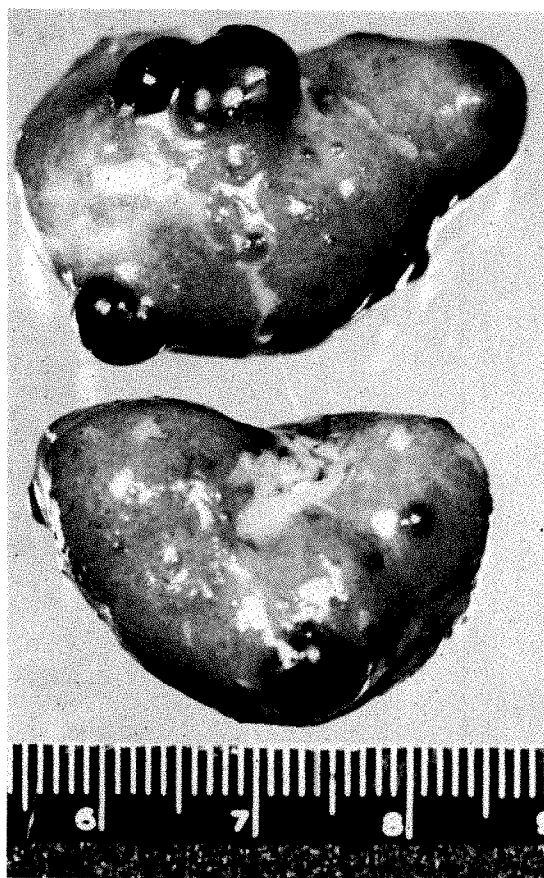


FIG. 1. Cystic degeneration of kidneys of a guinea pig killed 985 days after a single total body exposure to 650 r in air of Co⁶⁰ gamma radiation (LD_{75/20}).

with spleen extract, pertinent systematic studies have been performed.¹¹ From these studies it appears that spleen extracts accelerate first the recovery of the spleen and then, with a time lag of a few days, the recovery of the bone marrow.

This is illustrated in Figure 2, *A-D*: A comparison of *A* and *B* shows that as early as on the third postirradiation day recovery of the spleen becomes evident in the organs of the animals treated with spleen extract. *C* shows the bone marrow of a saline treated control and *D* of an animal treated with spleen extract on the seventh postirradiation day. Both appear equally affected by irradiation, *i.e.*, no incipient recovery could be demonstrated in the bone marrow of the extract treated animal. On the ninth day, however, also the bone marrow of the extract treated animals showed notable recovery, while the saline treated controls failed to show recovery as described in detail elsewhere.¹⁵

D. POSSIBLE USE OF SPLEEN EXTRACT IN THERAPY

The data presented so far suggested the possible use of spleen extracts for the treatment of lethal total body irradiation. Before, however, any attempt could be made to approach this problem from the point of view of human therapy, a number of problems required investigation. Most important was to find a suitable source of organ material permitting readily the preparation of large amounts of spleen extract. For this purpose the use of spleens from larger animal species such as dogs or calves was considered. Table 1 shows that dog spleens appeared to be the most suitable.

A comparison of the various spleen extracts listed in Table 1 from the point of view of spleen equivalent per injection, necessary to obtain a notable reduction of mortality in animals exposed to the LD_{75/20}, resulted in the average values of 500, 1,335 and 1,641 mg. for mice, guinea pigs and dogs, respectively.

From these figures it appears that the larger the animal species, the smaller is the content of protective factor per unit of organ weight.

E. OTHER CHARACTERISTICS OF RADIATION PROTECTIVE SPLEEN EXTRACTS

One problem of great importance to the application of spleen extracts in therapy consists in the possibility that such extracts might produce serious anaphylactic reactions. In the way these extracts have to be applied, they represent highly concentrated solutions of foreign proteins reaching concentrations of 10 per cent or more. So far only a few pilot experiments with respect to producing antigenicity have been performed such as sensitization of guinea pigs with mouse spleen extract and the study of the cutaneous reaction to intradermal injection of the mouse spleen extract. These preliminary investigations, however, did not show a significant cutaneous reaction.

A few pilot experiments concerning formation of precipitating antibodies were performed* on guinea pigs pretreated with mouse spleen extract. These pilot experiments failed to show precipitating antibodies with dilutions ranging from 1:10 to 1:500.

Furthermore, injection of 1 ml. of dog spleen extract into the ear veins of rabbits did not produce any adverse reactions, not even after repetition of this procedure with four weeks interval.

We hope to supplement these pilot studies with a systematic investigation on antigenicity of cell-free spleen extracts. While the pilot experiments do not permit any definite statement, they seem to permit the conclusion of at least a low antigenicity, since no obvious reactions were found in two animal species such as guinea pigs and rabbits, both well known for their susceptibility to anaphylactic reactions.

Attempts to characterize spleen extracts pharmacologically have so far been equally exploratory only: addition of spleen extract from mice, dogs and guinea pigs to a water bath in which an ileal segment of guinea pig intestine was suspended produced a contraction in 24 out of 30 tests. Circumstances beyond our control prevented

* We are indebted to LT J. H. Berrian, MSC, USN formerly at NMRI for carrying out these tests.

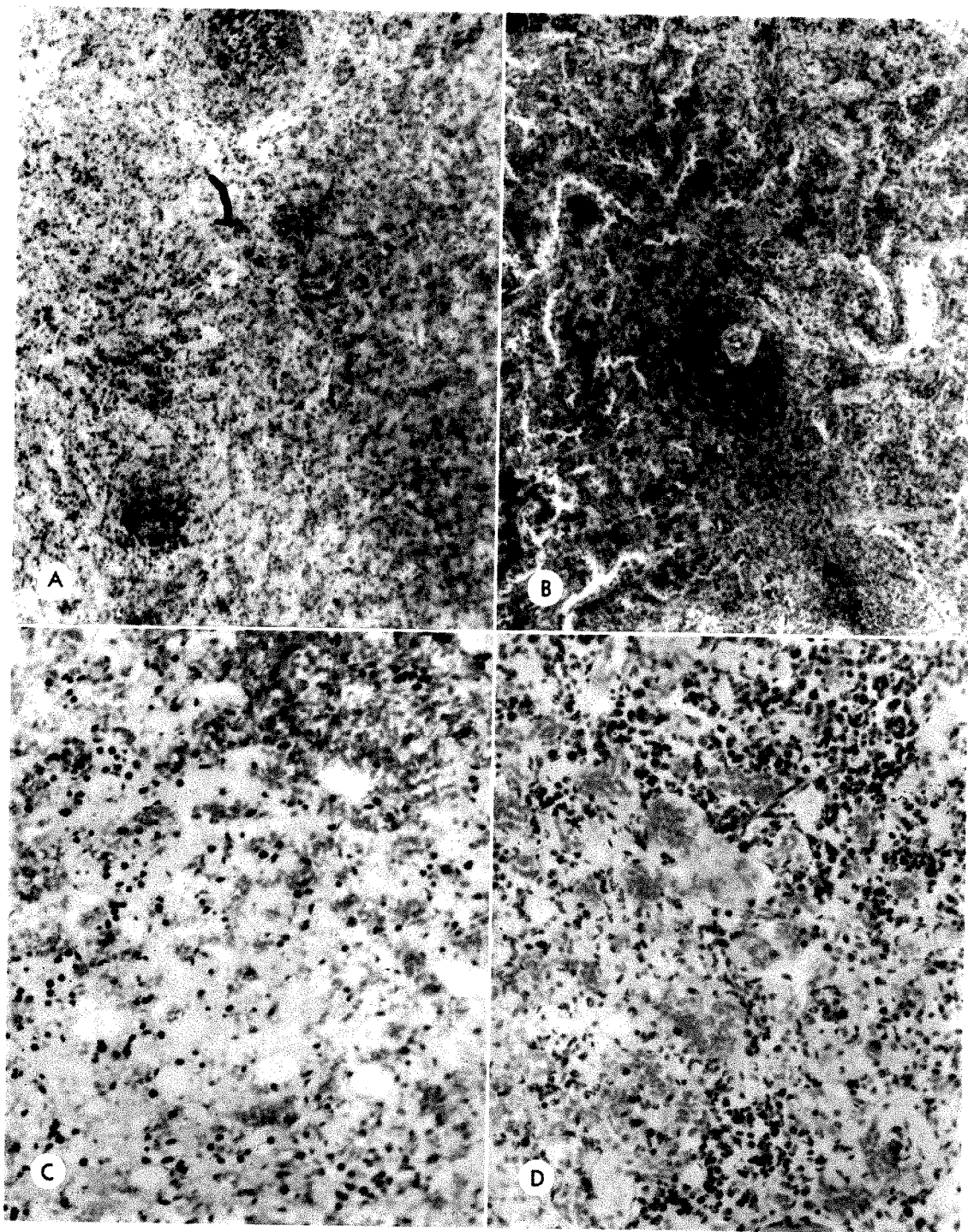


FIG. 2. Effect of cell-free guinea pig spleen extract treatment on hematopoietic tissues of guinea pigs after a single total body exposure to 650 r in air of Co^{60} gamma radiation ($\text{LD}_{50/20}$). (A) Spleen of saline treated control animal, 3 days postirradiation. Note decrease in cellular elements in both red and white pulp. Only indistinctly outlined remnants of malpighian bodies are seen. Hematoxylin-eosin, $\times 100$. (B) Spleen of spleen extract treated animal, 3 days postirradiation. Malpighian bodies though decreased in size show beginning of recovery. Compared with A, the cellularity of red and white pulp appears increased. Hematoxylin-eosin, $\times 100$. (C) Bone marrow of saline treated control animal, 7 days postirradiation. Sinusoids are congested with erythrocytes. Many gelatinous areas are present. Few granulocytes, reticulum cells and endothelial cells are seen. Hematoxylin-eosin, $\times 230$. (D) Bone marrow of spleen extract treated animal, 7 days postirradiation. Note similarity to C, indicating no recovery at this time. Hematoxylin-eosin, $\times 230$ (Reproduced with permission of *Acta haemat.*).

further elucidation of the nature of the contracting agent by the use of blocking agents. Injection of 0.5 ml. of guinea pig spleen extract into the femoral vein of a dog as well as repeat injection six weeks later did not produce a notable effect on either blood pressure or respiration.†

F. ATTEMPTS TO ISOLATE AND IDENTIFY CHEMICALLY
THE ACTIVE PRINCIPLE IN SPLEEN EXTRACTS

Pertinent studies have been carried out using paper chromatographic analyses of the spleen extracts of mice, guinea pigs and dogs.¹⁸ From these studies it appeared that all of these extracts contained 18 amino acids and 5 carbohydrates. A difference in the taurine content of spleen extract of mice and guinea pigs appeared of interest as a possible explanation for the differences in the spleen equivalent of these two extracts necessary for reduction of mortality.

In order to verify or disprove this contention, studies were carried out with taurine solutions varying from 12.5 mg. per cent to 45 mg. per cent. Amounts of 0.3 ml. were injected into mice and guinea pigs exposed to the LD_{75/20} days. No significant modification of radiation mortality was ascertained.

Chemical analyses of total protein content and nonprotein nitrogen content were performed.² No positive correlation between radiation protective effect and the total protein content was established. Somewhat better appeared the correlation between nonprotein nitrogen content and protective effect in various spleen extracts. From these and the paper chromatographic analyses, it is tentatively concluded that a polypeptide might be responsible for the protective action of spleen extracts. Compatible with such a contention is the result a pilot study on the effect of dialysis. This procedure appeared not to influence the protective action of dog spleen extract. On the basis of the characteristics of the membrane selected for this preliminary experiment, it can be assumed that the active principle must have a molecular size of two

thousand or greater. Further analyses using columnar chromatography are in progress. The results of these studies carried out together with Dr. Katz will be reported in the future.

SUMMARY AND CONCLUSIONS

1. Postirradiation treatment with homologous as well as heterologous cell-free spleen extracts in appropriate doses reduces radiation mortality (*e.g.*, in guinea pigs the LD_{75-80/20} is lowered to the LD_{40/20}).

2. This result can be obtained with treatment started after irradiation (during the latent period) when most chemicals fail to reduce mortality.

3. Treatment with cell-free spleen extracts is free from unpleasant side and deleterious late effects. Animals treated with such preparations gain weight and retain such weight gain until death.

4. Postirradiation treatment with cell-free spleen extracts avoids the inherent drawbacks of pre-irradiation treatment with chemicals.

5. Cell-free spleen extracts are effective if administered intramuscularly. This fact recommends them as a treatment method in emergencies because self-administration by a patient or administration by untrained personnel would be possible, if and when these extracts are used in human beings.

6. Cell-free spleen extracts can be produced in quantity, in view of the fact that homologous as well as heterologous extracts can be used. In this respect they are superior to the bone marrow grafts, since the use of the individual's own bone marrow appears necessary.

7. Cell-free spleen extracts can be stored for approximately one year without notable loss of activity. This represents another advantage over bone marrow, in as much as storage of viable bone marrow cells without loss of protective properties over longer periods of time is still a formidable technical problem.

8. Treatment with cell-free spleen extracts restores spleen *and* bone marrow. This proves the superiority of cell-free spleen extracts over marrow grafts also

† We are indebted to CDR S. W. Handford, MSC, USN of the Institute's staff for performing these tests.

from the functional point of view. Homografts of bone marrow restore bone marrow function by re-populating it "but spleen and lymph nodes show little evidence of return to normal."¹⁸

9. From the foregoing it appears that postirradiation treatment with cell-free spleen extracts appears to be the most practical and successful approach to the therapy of lethal total body irradiation so far developed by animal experimentation.

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PRELIMINARY REPORTS OF CHROMOSOME STUDIES DURING RADIATION THERAPY*

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THE mechanisms of the development of radiation leukopenia is unknown. The sternal bone marrow in the presence of leukopenia as a result of pelvic radiation therapy usually shows no evidence of depression.² Both Osgood⁶ and Lawrence *et al.*³ have apparently demonstrated that there is no indirect effect of radiation causing leukopenia. The available evidence, then, is that radiation leukopenia results from strictly local effects of the radiation.

Human cells in tissue culture have been shown to be extremely sensitive to radiation.⁷ This is apparently true *in vivo*, as recently demonstrated by chromosome abnormalities of the peripheral leukocytes of patients receiving radiation therapy and during the course of diagnostic radiologic study.^{1,8}

Makowski and McKelvey⁴ have shown that 40 per cent of patients in the University of Minnesota Hospital receiving radiation therapy for carcinoma of the cervix develop a leukopenia of 3,000 white blood cells or less. An attempt was made in this study to correlate the possible chromosome changes occurring in the peripheral leukocytes with the development of leukopenia in patients receiving radiation therapy for carcinoma of the cervix.

METHOD

The technique of Moorehead *et al.*⁵ was used for chromosome preparations from the peripheral blood. Leukocytic cultures were obtained within 48 hours after starting therapy and at weekly intervals during the course of therapy. If significant leukopenia occurred (below 3,000 white blood cells), several attempts were made to obtain ad-

ditional chromosome preparations. Thirty patients were studied but satisfactory preparations were obtained in only 36 per cent of the cultures. Unfortunately, in only 2 patients were satisfactory preparations obtained throughout the course of radiation therapy. In 15 other individuals at least one satisfactory chromosome preparation was obtained after the appearance of some degree of leukopenia.

RESULTS

Of the 30 patients studied, 19 had satisfactory initial chromosome preparations. In 4 patients, while the modal number of chromosomes was 46, only 54 to 68 per cent of the cells had this number. (This compares with 184 other unrelated patients who had chromosome preparations and of whom 278, or 98 per cent, had at least 80 of the cells in the modal number.) The other 15 patients had an apparently normal chromosome pattern (idiogram). Table 1 shows the chromosome studies of a patient with squamous cell carcinoma of the cervix. Another patient (J.S., squamous cell carcinoma of the cervix, LNS III) showed no significant alteration of chromosomes in five different cultures. Her lowest white blood cell count was 3,600.

Of the 15 other patients in whom satisfactory chromosome preparations were obtained, 7 showed apparently abnormal chromosomes in terms of chromosome breaks or decrease in the number of cells in the mode number (46) of chromosomes, after the fourteenth day of therapy.

Four other patients with a white blood cell count below 2,000 had multiple chromosome cultures done. Unfortunately, no

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TABLE I
E.L., AGED 24, SQUAMOUS CELL CARCINOMA OF THE CERVIX, LNS I

Days after Start of Therapy	2	6	16	19	22	24	Six Weeks after Therapy
Approximate tissue reaction midpelvis, 400 kv.*	250	650	1,800	2,020	2,360	2,500	
White blood cells	6,200	4,820	3,200	2,400	2,100	2,800	
Chromosome no. of modal cell	46	46	47	47	46	49	46
No. of cells counted	8	12	24	9	8	3	6
Per cent of cells in mode	84	82	52	55	37		82

* Unfortunately, the time of the drawing of the blood for chromosome study was not recorded in relationship to the daily radiation therapy.

satisfactory preparations were obtained. The serum from these same 4 patients was used in the leukocytic cultures of 6 other apparently normal individuals. Only two satisfactory preparations were obtained but these were apparently normal.

DISCUSSION

Because of the known sensitivity of the human peripheral leukocytes to radiation, it would be expected that chromosome alterations could be demonstrated in all patients receiving radiation therapy for carcinoma of the cervix. This does not appear to be so from this study. The failure rate of the leukocyte cultures increased from 37 per cent early in therapy to 89 per cent when significant leukopenia had

occurred, and to 100 per cent when the white blood cell count was below 2,000. This failure rate could be related to chromosome abnormalities.

The chromosome abnormalities could be the result of the faulty culture technique. This seems unlikely as such chromosome changes have not been seen in such significant numbers in our other investigations.

The sternal and iliac bone marrow should be studied. If the same chromosome abnormalities are present in the leukocytes from the sternal marrow, then an indirect factor would seem to be operating in radiation leukopenia. The one sternal marrow

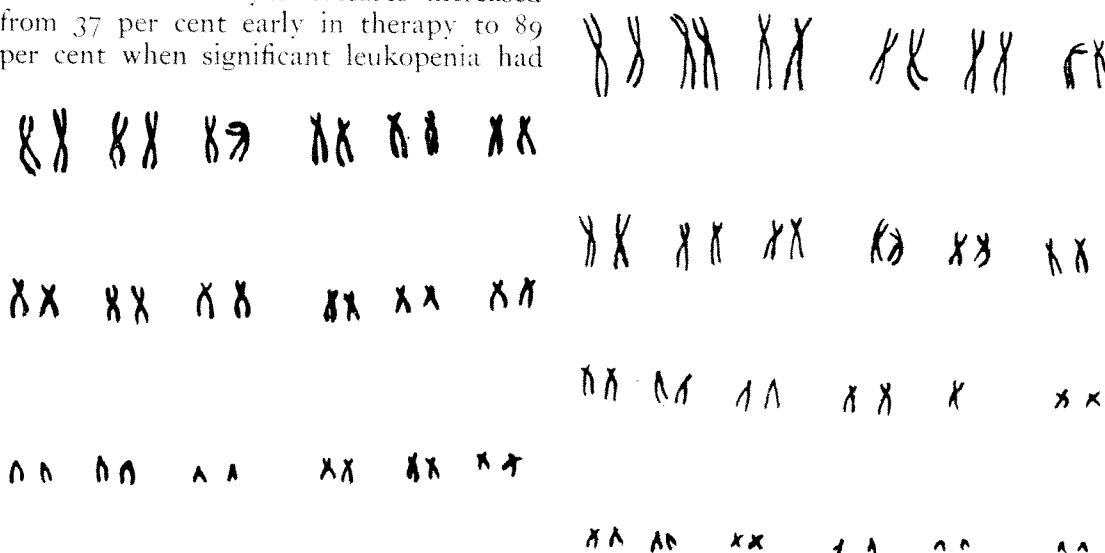


FIG. 1. A karyotype 24 hours after start of therapy (46 chromosomes).



FIG. 2. A karyotype 19 days after start of therapy (47 chromosomes). There are apparently two extra small acrocentric chromosomes and one less group E chromosome.

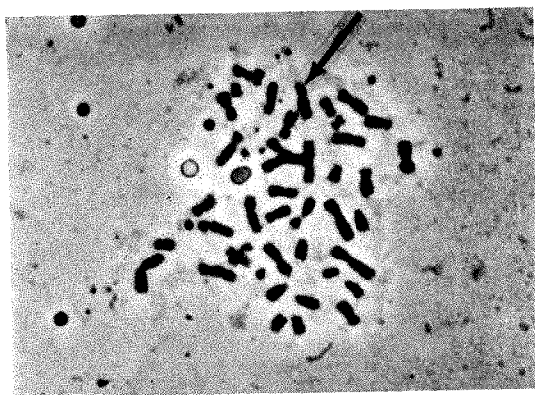


FIG. 3. Sixteen days after start of therapy (45 chromosomes). Arrow points to damaged chromosomes.

done on a patient with a white blood cell count of 1,400 showed no apparent abnormalities of the chromosomes. No satisfactory preparations were obtained from the peripheral blood.

The chromosome abnormalities in the leukocytes and leukopenia could well be unrelated. It may, however, be an explanation as to why the leukopenia occurs, as chromosome abnormalities may well bring about the death of the cell or its stem line. Puck⁷ has interpreted his data to indicate that radiation damage to the chromosome is the primary process leading to destruction of the reproductive ability of the cell.

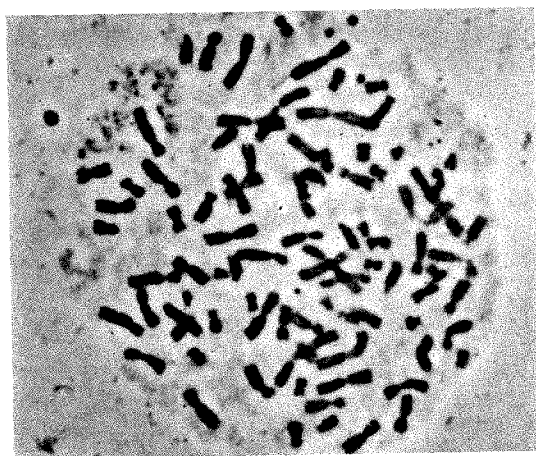


FIG. 4. Six days after start of radiation therapy (93 chromosomes). Such apparent tetraploid cells occur in normal leukocytic cultures in less than 1 per cent of the cells.

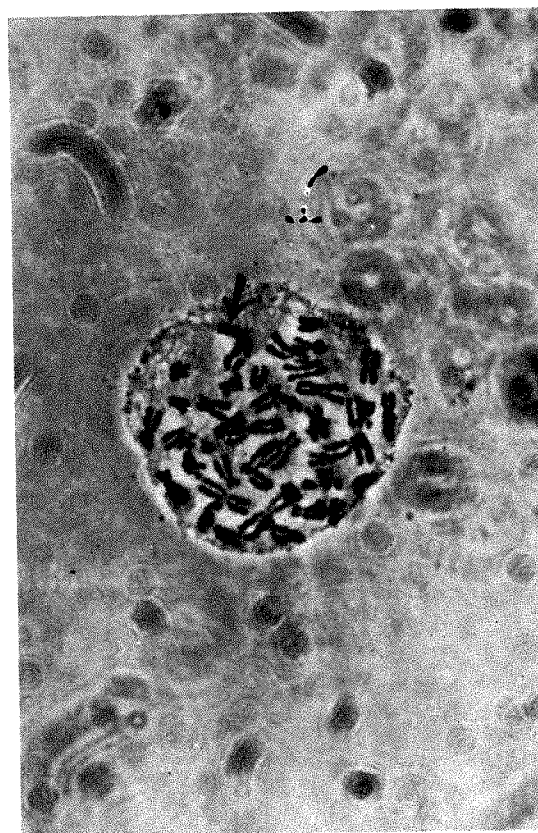


FIG. 5. Chromosome damage indicated by arrow (occasionally seen in normal cells) (42 chromosomes).

SUMMARY

A relationship appears to exist between chromosome damage of peripheral leukocytes and radiation therapy in cases of carcinoma of the cervix. The damaged



FIG. 6. Twenty-two days after start of therapy (48 chromosomes).

leukocytes may be in part an explanation of the leukopenia associated with radiation therapy.

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LOW LEVELS OF X-IRRADIATION AND THE EARLY MAMMALIAN EMBRYO*

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IT HAS been known for some time that x-rays are particularly damaging to differentiating tissues in embryos so that exposure at certain periods of development will result in a preponderance of correlating congenital anomalies. The earlier studies, using only high levels of irradiation, led to the erroneous assumption that these critical periods limited the time during which specific anomalies could be caused. Thus, it was stated that x-irradiation prior to 8.5 days in the mouse or rat either killed the embryos or the survivors were perfectly normal.

It was then demonstrated by Rugh and Grupp (1956 to 1960) that x-irradiation at any time from fertilization of the egg through this 8.5 day period might also induce severe congenital anomalies, using doses of 25 r or more. One anomaly, cerebral hernia or exencephaly, was chosen as the test condition and this was produced in embryos x-irradiated at any time prior to the completion of development of the central nervous system. This finding naturally led to a thorough study of lower levels of exposure on the very early embryos of the mouse, the data of which are here presented.

MATERIALS AND METHOD

CF₁ Swiss white mice were time-mated with males of the same strain and x-irradiated either at 0.5 or 1.5 days after conception. The mating times were such that there could be a disparity of as much as 9 hours in fertilization, but this would not alter the fact that at 0.5 day the embryos were still in the one-cell stage and those at 1.5 days were in the 2-cell stage.

The x-radiation facilities used consisted

of a single tube at 89 cm. from the level of the uterus, at 184 kvp., 30 ma., filtration of 0.28 mm. Cu and 0.50 mm. Al, half-value layer 0.6 mm. Cu, and a dose rate in air at the level of the uterus of 15 r per minute. Transposed to rads this was equivalent to 14.5 rads per minute to the embryos. The exposures used were either 5 or 15 r x-rays total, and in a single exposure. Following irradiation the mice were placed, along with the controls, in the same animal quarters used for all mice.

Following postirradiation intervals of 2, 6, 24, and 72 hours, x-rayed and control females were sacrificed by cervical dislocation and their entire reproductive tracts were quickly removed and fixed in Bouin's fluid. The entire oviducts and uteri were sectioned longitudinally and serially at 6 microns, stained in Harris' hematoxylin without benefit of counterstain, and searched for all stages of development. Some forty-five pairs of oviducts were thus sectioned, and twenty-eight other pregnancies were allowed to progress, and were terminated at 18.5 days for a study of the gross congenital effects.

EXPERIMENTAL DATA

The data from x-irradiated early pregnancies, which were allowed to develop almost to the time for delivery (18.5 days), are given in Table I.

This table shows that exencephaly (brain hernia) can be caused by as little as 15 r x-rays if delivered to the mouse embryo at 0.5 or 1.5 days post conception, or prior to the second cleavage of the fertilized egg. It has never been seen in the controls. Litter size shows a slight average reduction and there is a considerable increase in the

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TABLE I

	Controls	Experimentals (x-rayed)	
		0.5 Days Fertilized Eggs	1.5 Days
Age of Embryos			
Stage of Development			
X-Irradiation	0	15 r	15 r
Total Pregnancies	61	15	13
Total Implantation Sites	630	133	127
Total Normals (?)	591 (94%)	107 (81%)	112 (88%)
Total Exencephalies	0	1 (0.7%)	3 (2.3%)
Total Resorptions	37 (5.7%)	25 (19%)	11 (9%)
Total Dead	2 (0.3%)	0	1 (0.7%)

percentage of intrauterine death and resorptions. In most regards the 0.5 day embryo (pre-cleavage) appears to be more radiosensitive than it is 24 hours later, at the 1-2 cell stage. The percentage of normal fetuses found is indicated with a question mark because, while those of the controls are indeed normal, those from litters containing exencephalies are questionably normal. It is believed that exposure sufficient to cause this severe central nervous system anomaly must be sufficient to cause lesser effects in all litter mates, even though not readily demonstrable.

A preliminary study was made on 12 pregnancies which had been exposed to 10 r x-rays at 0.5 days post conception, or prior to the first cleavage. These pregnancies were allowed to progress and at 18.5 days were examined for development. It was found that of the 108 implantations, 85 (or 78.7 per cent) appeared to be normal while 23 (21.3 per cent) had died at an early stage and were resorbed prior to differentiation. This figure is 15.6 per cent above the 5.7 per cent expected from this stock among 630 control implantations. The average litter size, counting all implantation sites, was 9.0 as compared with 10.3 for the controls. These figures suggest a loss at such an early stage that no implantation site was established. No gross anomalies were found. However, there was considerable variation among the irradiated pregnancies so that implantation sites ranged from 1 to 12, and resorptions

within single litters ranged from 10 per cent to 56 per cent. These variations in response to a uniform field of x-irradiation are probably an indication of genetic (biologic) variability in radioresponsiveness.

Since 10 r seemed to destroy some embryos prior to implantation, it became necessary to investigate even lower dose effects on the very early stages on a cytologic basis, and within hours of irradiation. A total of 49 pregnancies, involving 302 implantation sites comprises the cytologic data for Table II, revealing the effects of only 5 r x-rays delivered after fertilization of the egg but prior to the initial cleavage (at 0.5 day).

From the data of this table it appears that even 5 r will delay the first cleavage since the percentage of the controls in the 2-cell stage was always statistically much higher than for the parallel x-irradiated embryos. Further, the cytologic study revealed that there was a considerable increase in the number of abnormal early stages, most evident 24 hours after exposure. This means that some fertilized eggs did not reveal the irradiation damage until the time of cleavage, since at 6 hours there were 6 per cent and at 24 hours there were 20 per cent abnormalities. In another group of pregnancies, which were exposed to 5 r, an analysis of some 80 implantation sites at 18.5 days gestation showed an increase of 14.3 per cent in the resorptions over the controls. Thus, with pre-implantation death plus the post-implantation death

TABLE II

EFFECT OF 5 RADS EXPOSURE OF THE MOUSE EMBRYO AT 0.5 DAYS POST CONCEPTION

Condition	Mice	Pregnancies	Embryos	1-Cell Stage	2-Cell Stage	Abnormals
0.5 Days	Controls	10	66	56(85%)	10(15%)	0
+						
6 Hours	x-rayed	14	89	84(94%)	0	5(6%)
0.5 Days	Controls	14	78	11(14%)	65(83%)	2(2.5%)
+						
24 Hours	x-rayed	11	69	21(30%)	34(50%)	14(20%)

with resorption, there is considerable loss of embryos prior to neurogenesis, even at low levels of exposure.

The cytologic data cannot be statistical, and it must be admitted that occasionally there are disintegrating early embryos even among the controls. However, the high (20 per cent) early disintegrations of mouse embryos following 5 r as seen in sections of whole oviducts and uteri strongly suggest that radiations may be the causal factor. The most frequently observed anomaly is fragmentation or disintegration of the fertilized egg, or early cleavage stage. The pinched-off fragments of cytoplasm may or may not contain the male or the female pronuclei. In those cases where the pronuclei remain in the reduced cytoplasm of the fertilized egg, it is believed that the resultant fetus would be stunted. Such a finding would be expected from comparable extirpations in experimental embryology with poikilothermic forms. However, where the two pronuclei are discarded in the extruded cytoplasm, the remaining cytoplasmic (enucleated) mass could not be expected to survive. Other effects on these early stages include swollen, indistinct, or even pyknotic nuclei; hyperchromatic or unevenly staining cytoplasm suggesting some denaturation processes and phase degeneration; vacuolization of the cytoplasm; separation of blastomeres; and, in mitotic figures, lagging and "sticky" chromosomes.

When embryos in the 2-cell stage are exposed to 15 r and examined at the time

of expected implantation, at 4.5 days, some will give evidence of radiation damage in the form of cell vacuolization; giant cells with extra sets of chromosomes; uneven cell growth; dissociation of cells; and some cases of complete disintegration of the embryo. Confirmation of these cytologic effects may be in the lowering of the expected total litter size or implantation sites, when large numbers of pregnancies are considered. The fact that these cytologic effects are demonstrable in material prepared in exactly the same manner as the controls suggests that such a low level of exposure as 5, or 15 r can destroy some mammalian embryos in the very earliest stages of development.

DISCUSSION

The term "low dose" of ionizing radiation has different connotations in different disciplines. To the therapist it might mean 200 r, to the Civil Defense authority it might be 50 r, to a histologist it could be less than 22 r since at that level half of the exposed spermatogonia are destroyed (Russell, Russell, and Oakberg,¹⁹ 1958); to a hematologist it could be 12 r which causes a mild lymphopenia in 2 hours; to the diagnostician it might be 1-5 r; or to a geneticist it might be a single ionization believed to be sufficient to cause a mutation. The embryonic LD₅₀ is currently being established, but it is safe to predict that there may be at least a ten-fold difference between the early stages in development and the fetus just before delivery. Thus,

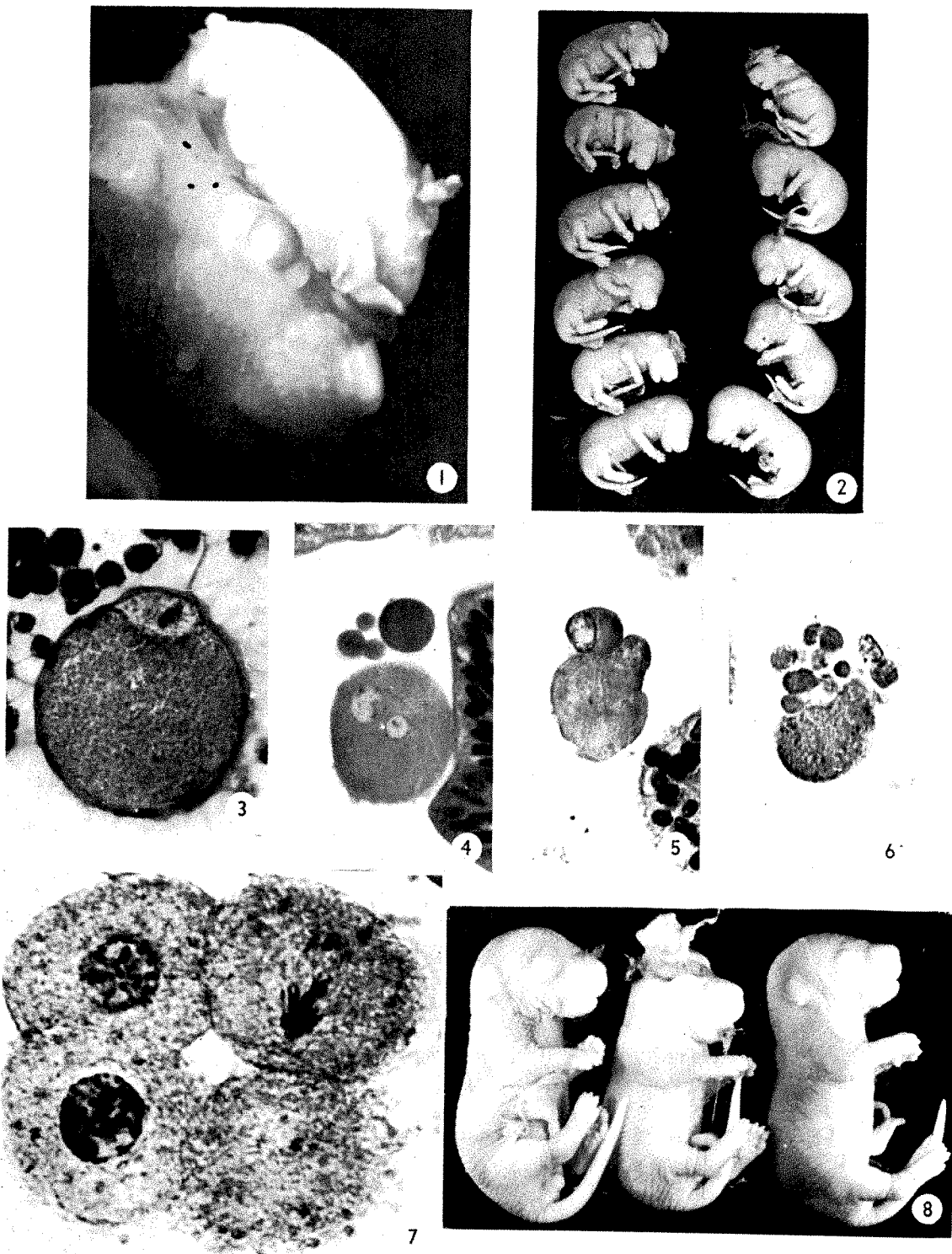


PLATE I

FIG. 1. Typical brain hernia, exencephaly, showing protrusion of mesencephalon through the cranial roof.

(Explanation completed on facing page)

"low dose" must also consider the target object. If exencephaly can be produced at all in an embryo exposed to 15 r, it is a question as to whether such a dose may justifiably be called "low" for embryos.

Even with adult organisms the concept of a low dose may be further revised downward. Recently, Dr. Dorothea Miller of Chicago found, rather by accident, that a certain cross of hybrid mice normally have audiogenic seizures which may be brought on or accentuated by exposures to gamma rays totalling only 1.2 rads at 24 mrads/hour for an 8-hour day for a one-week period. Electroretinograms reveal damage to embryos when the eyes are not grossly suspect (Noell, unpublished). An exposure of 15 r to rat embryos at 1.5 days post conception caused effects on their subsequent learning capacity, and the females were more affected than the males (Kaplan, unpublished). Thus, it should not be surprising that 5 rads has an effect on the mouse embryo, particularly in its early stages.

When irradiated fetuses are regarded as "normal" because they do not reveal any gross anomaly, such as exencephaly, we are stretching the limits of the word. There is reason to believe that every member of a litter is similarly exposed to ionizing radiations when the source is penetrating, high voltage, filtered x-radiation. However,

there are variations in response within any litter, and this would be expected in any biologic experiment where genetic variables are involved. Thus, a litter mate next in the uterus to one with exencephaly, might survive and appear "normal" by any gross analysis. However, it has been shown that most of these individuals are reduced in size, stunted to a degree, indicating some deficiency during development. Such deficiencies are expressed as abnormal, reduced (microphthalmic), or absence of eyes, microcephalia, anencephalia, deformed appendages, etc. Currently there are five independent but correlated studies being made on low dose effects on the early embryo, studies which are neither histo- or cytologic. They include electroencephalography, electroretinography, psychologic behavior tests, fertility tests and long term sequelae. While a person with an I.Q. of 80 or 170 might be considered normal, the difference between these extremes could be the result of some congenital insult such as by x-irradiation. Thus, we are striving to determine whether in fact a threshold of x-irradiation exists for the embryo beyond which even functional tests would be negative.

Russell (1950-1957) stated that if the mouse embryo is exposed to 200 r prior to implantation (*i.e.*, at 4.5 days) there is an increase in the prenatal mortality but that

This can be produced by x-irradiating the germ cells of the male or female before mating, or by direct exposure of the embryo at any time prior to the completion of neurogenesis.

FIG. 2. Entire litter as seen in bicornuate uterus, showing 5 exencephalies in litter of 11, following exposure to high level of 150 r at 8.5 days gestation, during neurogenesis. Congenital anomaly similar to that in Figure 1.

FIG. 3. Normal mouse egg at moment of fertilization, showing sperm head penetrating the cortex. Period of maximum radiation sensitivity.

FIG. 4. Exposure to 5 r at time comparable to that in Figure 3 showing fragmentation of the egg. Note remaining cytoplasm with male and female pronuclei apparently intact. Embryonic protoplasm reduced.

FIG. 5. Fertilized egg exposed to 5 r at stage comparable to that in Figure 3. Note both male and female pronuclei being everted. This would leave a nonviable mass of protoplasm.

FIG. 6. Fragmentation of egg due to 15 r at stage comparable to that in Figure 3. The embryo could hardly survive this extent of damage.

FIG. 7. Four-cell stage following 15 r at stage comparable to that in Figure 5 showing lagging chromosomes of mitotic figure in upper right blastomere two days after irradiation.

FIG. 8. Three members of litter which had been exposed to 15 r at 1.5 days, or at stage comparable to that in Figure 9, Plate II. Note exencephaly of middle fetus. Others slightly stunted.

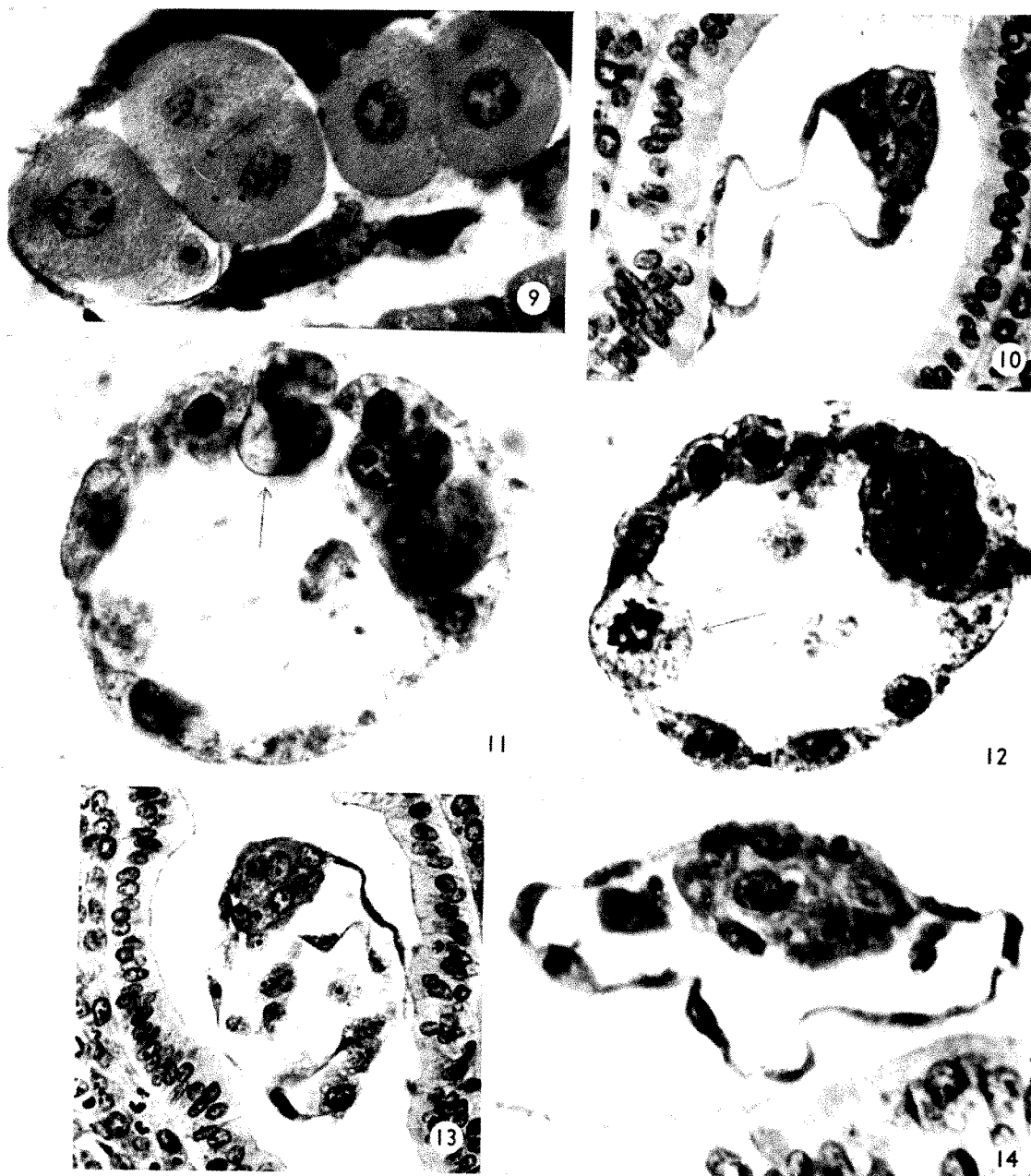


PLATE II

FIG. 9. Normal mouse embryos (3) at the 1- and 2-cell stages showing normal nuclei and clear cell boundaries.

FIG. 10. Normal mouse embryo at moment of implantation at 4.5 days post conception, also a radiosensitive stage.

FIG. 11. Embryo x-rayed at stage comparable to that in Figure 9, with 15 r, showing enlarged cell with large vacuole (arrow).

FIG. 12. Embryo similar to that in Figure 11 but showing giant cell with extra chromosomes (arrow).

FIG. 13. Result of x-irradiation with 15 r at 1.5 days, or stage comparable to that in Figure 9. This should have the appearance of Figure 10 but note necrotic and discarded cells within the blastocoelic cavity. If this could survive, it would be seriously deficient in cells.

FIG. 14. Mouse embryo x-rayed at the 2-cell stage with 15 r and seen at 4.5 days when it should be implanting, as in Figure 10 above. Note pyknotic nucleus of extruded cell within blastocoel, as well as in blastodisc. Such an embryo might survive but would be deficient in cellular elements.

100 per cent of those which survive implantation are "normal" with respect to their external characters. Otis and Brent (1952) confirmed these findings. However, Rugh and Grupp (1959, 1960) found that exposure prior to organogenesis caused mouse embryos to be stunted though usually they were topographically normal. This means that the irradiation-damaged cells were phagocytized or discarded, leaving enough undifferentiated cells for the embryo to reconstitute a topographically well balanced, but reduced, individual. Hicks^{1,2,3} described the effects of x-irradiation on the rat embryo as causing deficiencies, deletions, extirpations, and death of cells, so that embryos were all lacking in certain central nervous system requisites. The effects were never the same on litter mates simultaneously exposed, but the common denominator was cell loss. This necrosis of the developing cells resulting in reduced development of the central nervous system was first described for the developing amphibian in 1949, 1950 and 1953, and particularly for the retina in 1955 and 1956 by Rugh. Neuroblasts are particularly radiosensitive and the embryo has abundant neuroblasts even until after birth.

After neurogenesis is completed, congenital anomalies of the central nervous system cannot be caused by x-irradiation. During neurogenesis the abundant neuroblasts are radiovulnerable so that a high percentage of anomalies can be produced, but with relatively high levels of x-irradiation. However, when the 1- or 2-cell embryo is exposed, and a single cell is damaged, it constitutes all or half of the precursors of all of the cells of the future fetus, so that the effects are more inclusive. If the radiation-damaged blastomere of the 2-cell stage is discarded, the remaining cell could presumably give rise to a complete, but much reduced fetus. The earlier workers, using 200 r, must have killed off the vast majority of early embryos, so that survivors with congenital anomalies were not found. *Thus, it seems that high doses which kill may be better for the race than*

low doses which maim and allow the survival of the resultant congenital anomalies. Current studies are in progress to determine whether low level exposures of the embryo at any stage will affect its subsequent fertility. While congenital anomalies caused by x-irradiation during development cannot be inherited, the simultaneous exposure of the developing gonads could well have genetic sequelae which should be investigated.

SUMMARY AND CONCLUSIONS

1. The newly fertilized egg of the mouse or the 1-2 cell stage (at 24 hours) has been x-irradiated to low levels of 5 and 15 r, and the embryos and fetuses examined for sequelae.

2. While it is believed that every early embryo subjected to x-rays is damaged to some extent, the percentage of the "apparently normals" following 5 r and 15 r at these early stages was reduced only to 88 per cent and 81 per cent, respectively.

3. The percentage of early deaths and resorptions was increased over the controls (of 5.7 per cent) to 19 per cent among those irradiated before cleavage and to 9 per cent among those irradiated during the first cleavage.

4. *Exencephaly*, or brain hernia, which is a severe central nervous system congenital anomaly caused, among other traumatic conditions, by x-irradiation prior to the completion of neurogenesis, was also found following only 15 r at both 0.5 and 1.5 days post conception. Thus, this anomaly can be caused by x-irradiation long before any neuroblasts are present, and, in fact, before cleavage so that the so-called "critical period" for central nervous system anomalies must extend back to fertilization. These particular anomalies cannot be produced by x-irradiation after 10.5 days in the mouse, which corresponds to about 4 to 5 weeks for the human embryo.

5. Even after 5 r exposure there was some evidence of delay in the early cleavages, and an increase in the percentage of early abnormals, cytologically determined.

6. Some of the cytologic effects of x-rays on the early embryo were: fragmentation, separation of blastomeres, elimination of protoplasm as blebs, elimination of one or both pronuclei, pyknosis of the nuclei, swelling, vacuolization, hyperchromaticity, and staining evidence of phase degeneration.

7. *No threshold level of x-irradiation has been determined* for central nervous system congenital anomalies of the very early mouse embryo. Since exposures of 5 r can cause severe anomalies among the survivors, even lower levels of exposure are currently under investigation.

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THE INFLUENCE OF THE TIME FACTOR ON THE DOSE-RESPONSE CURVE*

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THERE are many examples in the literature of dose-response curves for radiation administered in a single session, usually shown as sigmoids against either dose or log dose, but there are none for the usual clinical technique of multiple daily treatments. In practice, radiotherapists have tacitly assumed that both the shape and slope of the response curve, whether for therapy of tumor or for tolerance of normal tissue, are unchanged as the number of treatments is increased from one to many. In comparing doses given in different over-all times, it is the custom to draw a line through one of the doses parallel to an appropriate time-dose line drawn on log-log paper and judge the relative value of the second dose according to its position with respect to this line. If it lies above the line, the conclusion is that it should result in correspondingly greater effect than the first dose; if below, in less. It has been pointed out in an earlier publication³ that this procedure is valid only if the dose-response curves for the two over-all times are parallel curves against log dose. This has not been demonstrated.

Equally missing is information about the effect on the dose-response curve of another aspect of the time factor; namely, fractionation, by which is meant the number of treatments into which the total dose in an over-all time is broken. Thus it involves the size of the treatment dose in relation to the interval between treatments. All the time-dose lines based on clinical material which have been determined to date are for so-called "daily" treatment. While there is evidence from the experimental laboratory that fewer and larger treatments might be more effective,^{4,5,12} therapists are reluctant

to abandon techniques with—as a result of long experience—predictable results, in favor of a new technique about which there is no clinical information. In other words, the information is qualitative only, and without quantitative relationships it is impossible to convert doses from one technique to another, or to compare doses given under different time conditions.

In 1956 a study was begun to provide information about the dose-response curve for variations in fractionation and over-all time which would be comparable to those used clinically.

MATERIAL AND METHOD

The test object chosen was spontaneous mammary adenocarcinoma in C₃H mice. The mice were received from the Roscoe B. Jackson Memorial Laboratory in Bar Harbor, Maine, in lots of about 10 per week. They were between 8 and 10 months of age and bore spontaneous tumors on arrival. Groups of four were housed in stainless steel cages with cedar or pine shavings as bedding. They were fed Purina laboratory chow and had access to water at all times. The cages were cleaned three times a week and autoclaved when the last occupant died. In the latter part of the experiment, the animal room was air-conditioned and the food kept off the bottom of the cage by wire hoppers. Mice were allowed a few days after arrival to become accustomed to their new environment before starting treatment.

No tumors outside the arbitrary limits of 8 to 20 mm. in diameter were treated. Larger tumors had so little possibility of being cured that they did not constitute a good test of technique. Smaller tumors usu-

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ally disappeared early in the treatment series and it was difficult to be certain that any remaining tumor cells were included in the treatment field, particularly because of the ease with which a tumor can be moved over the surface of the mouse's body to a new position. Furthermore, small cysts occur occasionally in these mice and might be treated by mistake as a tumor, since all tumors were not biopsied before treatment. Of 200 biopsied, however, only 2 were not reported adenocarcinoma, so any error resulting from lack of biopsies should be negligible, particularly since cysts should be recognized during a long follow-up period.

In the early part of the experiment, a treatment plan was assigned to a mouse by choosing one from among a group of shuffled cards held face down. Later it was discovered that in spite of this attempt at randomization the tumor sizes were not distributed with satisfactory uniformity among the various treatment groups in view of the extremely important influence of tumor size in determining outcome of treatment. Therefore, during the last year of the experiment the treatment cards were divided into three groups according to tumor size and treatment for a mouse was chosen from the appropriate group after measurement of the tumor.

The hair was clipped over the tumor to aid in accuracy of measurement and of set-up. The tumors were measured by fitting them to a series of holes in stiff paper. The mouse was immobilized for treatment by wrapping it in wire mesh which was cut away over the tumor; a leg was brought through this opening and taped to the mesh. The treatment field allowed a 5 mm. margin around the tumor; the lead shield around this covered the entire mouse, which was supported by a cardboard carton.

The experiment was begun with an old therapy machine run at 190 kvp., 20 ma., 0.25 mm. Cu plus 1 mm. Al filter, 20 cm. distance, half-value layer 0.7 mm. Cu. Midway through the experiment this had to be

replaced, and the remainder of the work was done with a machine run at 220 kvp., 20 ma., 0.25 mm. Cu plus 1 mm. Al filter, 20 cm. distance, half-value layer 0.8 mm. Cu. The tube was calibrated once a week with a Victoreen condenser r-meter; a monitor chamber checked constancy of output during treatment. The dose rates were 6 to 9 r/sec. (Air doses are given throughout this report.)

All treatment plans were repeated during the entire five year period of the experiment in an attempt to minimize the influence of such variables as skill of handling the mice, dosage errors from calibration or set-up, change in mouse or tumor, housing conditions, etc.

After completion of treatment the mice were examined once a week until their deaths. Notes were made of reactions, tumor sizes, and any other observations considered pertinent, both during treatment and throughout the follow-up period. As a rule, mice were allowed to live until natural death, but occasionally when tumors grew very large and/or mice were in very poor condition, they were killed with ether. This was never done when the treated tumor was thought to be cured, but only when the growing tumor gave certain evidence that the treatment had failed. The follow-up period ranged from a few days to 223 days after completion of treatment, the median being 36 days. The short follow-up on some of the mice was a cause of concern, although it was noted that some tumors palpable at the conclusion of the treatment series later disappeared, while some which could not be detected at this time later recurred. Since there were 56 of the former and 58 of the latter scattered throughout the treatment plans, it was thought that this would probably average out.

During the five year period from January, 1956, to December, 1960, a total of 1,458 mice was treated for this study. Of these, 28 per cent died during the first three weeks of treatment and an additional 8 per cent during the fourth week of the 25-day

group. In 96 mice it was impossible to be certain whether the tumor was present or not at the last examination; these were called indeterminate and dropped from the analysis. Finally, 9 mice were dropped by the statistician because they were in groups too small to be used. This left 828 mice on which results of treatment could be evaluated.

RESULTS

A cumulative normal distribution curve becomes a straight line when plotted on probability paper. This makes the data easier to handle and results are presented in this form. The question then was whether to use dose or log dose as the abscissa. Time-dose curves in clinical use are based on log dose and it is the slope of the curve under these conditions which is of interest, so log dose was used. Actually, it makes little difference which unit is used, except near the extremes of the sigmoid.

The results of the experiment were analyzed, using a modified probit analysis. First, the cure rates were corrected for tumor size distribution. Then, the straight line best fitting the experimental points was obtained by the method of least squares. Figure 1 shows the dose-response curves obtained for the six techniques studied; namely, treatment two, three, or five times a week to 18 days or to 25 days. Tumor control means complete and permanent disappearance of the tumor, as determined by palpation. It proved impossible, or at least impractical, to obtain complete dose-response curves from 0 to 100 per cent because of the high mortality among the mice when the doses were extremely high, aside from the fact that supralethal effect might be expected. However, a range of response broad enough to answer the questions raised was achieved.

For each technique, the slope of the straight line in an over-all time of 18 days was compared with the same fractionation carried to 25 days. The probabilities of finding the differences of slope resulting from this experiment if the total population

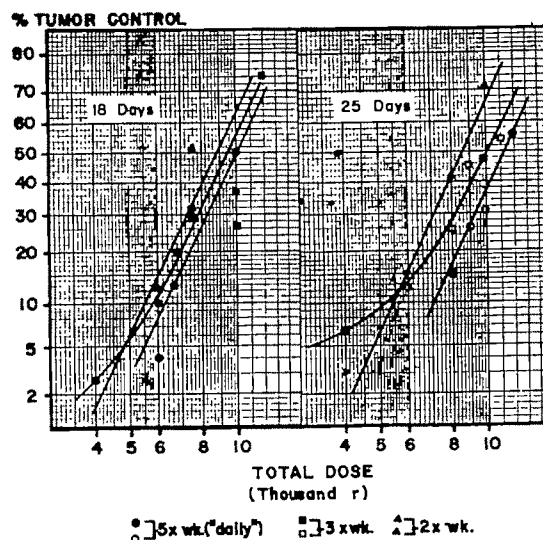


Fig. 1. Per cent tumor control among those mice completing the treatment plan begun by them. Cure rates have been corrected for tumor size distribution. Equations for the lines for daily treatment are:

$$y = 6.9624x - 1.9336 \text{ (18 days)}$$

$$y = 6.9624x - 2.3610 \text{ (25 days)}$$

where $x = \log(\text{total dose}/1,000)$; $y = \text{transformed cure rate}$.

Cure rate is transformed to z by

$$r = \int_{-\infty}^z \frac{1}{\sqrt{2\pi}} e^{-(t^2/2)} dt;$$

z is transformed to y by $y = z + 5$

would yield parallel lines are 0.15, 0.48, and 0.76, respectively, for treatment two, three, and five times a week. The differences are not statistically significant and the conclusion that over-all time does not change the slope of the dose-response curve within the limits used here would seem to be justified. The only effect of increasing the over-all time is a shift of the curve along an axis. It follows that isoeffect lines on log-log paper like those in common use in clinical radiation therapy departments should be parallel for all response levels below supralethal effect within reasonable limits of over-all time. The procedure described earlier for comparing doses given in different over-all times is, therefore, valid.

Since the differences between slopes for the two over-all times were not significant,

the slope shown in Figure 1 is the pooled slope for daily treatment. From these curves the time-dose line for any specified cure rate of these mouse tumors can be drawn. For daily treatment the slope of this line is 0.43, that found for human adenocarcinoma is 0.33.³ The slope of the time-dose line for isoeffect is a measure of recovery, and there would seem to be no reason to expect that adenocarcinoma, or any other cell type for that matter, would necessarily show the same recovery in mice as in humans. Indeed, Berg and Lindgren² found a slope of 0.33 for skin tolerance in rabbits, compared to 0.27 found for human skin.³ Recovery from whole body irradiation has also been shown to vary from species to species.¹³ Since the slope determined in the present experiment is based on only two points, no statistical test can be made of its reliability. It is presented here as a tentative slope only, requiring corroboration or correction.

If the technique of treatment were twice a week instead of daily, these dose-response curves would yield a time-dose line with a lower slope, but the fit of the experimental points is not good enough in this case to warrant its quantitative determination. We can say, however, that the advantage of protraction is increased when treatment is twice a week instead of daily. To put it conversely, if treatment is protracted, the advantage of using fewer and larger treatment doses is even greater than when the over-all time is short.

The data were next examined to determine what effect a change in fractionation has on the dose-response curve. Referring again to Figure 1, obviously here also there is a shift of the curve along an axis, fewer and larger treatments requiring a smaller total dose to reach a given cure rate than many smaller treatments. The differences in slopes between the curves for treatment five times a week and for twice a week are not significant, the probabilities of obtaining them by chance being 0.16 and 0.73. Again we may conclude that these curves are also parallel. The curve for treatment three times a week yields ambiguous re-

sults. In two instances the differences are significant ($p=0.03$ and 0.05) and in two they are not ($p=0.34$ and 0.67). Furthermore, the points seem to lie on a curved line in this instance, not on the straight line fitting the other techniques. A statistical test for curvature, however, did not result in significance, and these data, therefore, do not warrant the conclusion that the relationship is a curve for these coordinates. The failure to demonstrate this may be due to the fact that the data do not extend to low enough dose and response levels. To accomplish this, however, would require such very large numbers of mice that the time and work involved make it almost prohibitive. This same fact may also explain the ambiguous results of the test for parallelism, the result depending on the level reached.

In the last months of this experiment additional information came to light on this subject. Barth, Boehmer, and Wachsmann¹ transplanted ascitic fluid from the abdomens of mice bearing Ehrlich's carcinoma to the tails of other mice. These transplants were irradiated, using different fractionation techniques. Total doses were adjusted to give the same skin reactions, based on results obtained in an experiment on tolerance of pigs' skin. A reduction of 15 per cent for treatment every other day and of 25 per cent for treatment every third day was made from the dose used with daily treatment. Over-all time was essentially constant, so the interval between treatments increased with the size of the treatment dose, as in the present experiment. In spite of the unequal total doses, tumor response was greater for 340 r or for 425 r every 48 hours than for treatment daily or every third day. It is at these dose levels that the optimum appears in Figure 1, although it disappears at higher doses. The two experiments are not only in agreement, but a differential effect has been demonstrated, increased tumor response being shown for equal skin reactions.

The explanation for these results is not clear. A change in the shape of the dose-response curve would indicate a change in

the mechanisms bringing about the response. Early in the experiment when the progressive deviation of the line for treatment three times a week from that for daily treatment was noticed, it was reported.⁴ At that time it was suggested that the differences might be due to variations in radiosensitivity of the tumor cells at different times after irradiation, resulting from differences in mitotic activity. The German workers,¹ also, suggest that their results could be due to the fact that mitotic activity in their tumor is at a maximum 48 hours after irradiation, according to Luther. The latter, however, used doses of 1,000 r and the larger the dose, the later the maximum, as shown in Figure 2* for the C₃H mammary adenocarcinomas. They probably did not have a maximum for their lower doses. It is possible that mitotic activity is the correct explanation, but neither experiment proves this.

There are many other experiments which show a cyclic variation in response to radiation with increasing interval between doses. These seem to fall into two groups, those involving intervals of hours and those with intervals of days: Lethality of mice to whole body irradiation⁹ and chromosome breakage¹¹ showed minimum dose-response at 5 and 4 hours, respectively. Lymphoid tumor development in mice was a maximum for irradiation at intervals of 4 to 8 days, although no variation in terms of days was found for mortality.⁸ Other examples could be cited, but these suffice to make the point that there seem to be two types of cyclic variation in dose-response. It is suggested that one may be due to variations in radiosensitivity of the cells themselves during the recovery phase, as shown in Elkind's⁵ work on cells in culture, and the other, perhaps including the present example, may be due to the tumor bed, and is seen *in vivo*. As Koller¹⁰ and others have described the part played by the tumor bed in determining radiation effect, part of the action of radiation on the tumor is brought about through

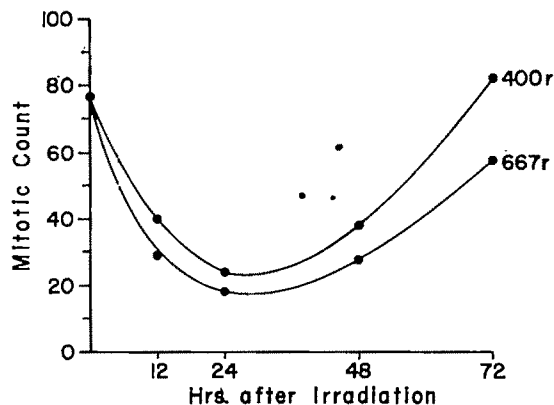


FIG. 2. Number of tumor cells seen in mitosis during a three minute counting period at various times after radiation doses of 400 r and 667 r.

an indirect action excited in the tumor bed or host.⁷ When the treatment dose is too large, this action is suppressed. When the interval between doses is too short, its operation is curtailed, and, when it is too long, cell replacement cancels its effect. This would explain the curved line, the technique becoming an optimum only when the proper balance between size of treatment dose and length of treatment interval is attained.

There is nothing in this theory to imply that an optimum can occur only for 48-hour intervals; the proper balance should be attainable for other intervals. Examination of the data in Figure 1 shows that a similar curve is suggested by the points for treatment twice a week to 25 days. Again, failure to demonstrate it conclusively may be due to the lack of very low dose-response levels. Garcia's⁶ data on carcinoma of the cervix show a change in slope for very long over-all times where the treatment dose becomes small in relation to the 24-hour interval between treatments.

The remainder of the results presented here can be explained, qualitatively at least, in terms of size of treatment dose. The influence of this factor is shown most clearly in the experiments on mammalian cells in culture, those of Elkind,⁵ for example. He has shown that, except for low doses, survival of cells *in vitro* decreases exponentially with size of dose. The effect of a second dose varies with the interval if given

* These curves were determined by Dr. John W. Budd, pathologist at Hollywood-Presbyterian Hospital, Los Angeles, California.

during the first few hours, but for a dose given between 12 and 30 hours after the first one, the effect of the first dose is repeated. After 30 hours replacement of cells begins, and the effect is less. Thus, for treatment with intervals of 12 hours or more, the effect is greater the larger the treatment dose, providing the interval is not long enough for replacement to overcome the influence of dose size. Applying this to the results shown in Figure 1, we see that for the larger treatment doses used in treating twice a week to the same total dose in the same over-all time the effect is greater than for daily treatment with small treatment doses. Treatment to the same total dose with the same intervals requires larger doses when the over-all time is 18 days than when it is 25 days, again with greater effect. Thus, both fractionation and protraction effects are explained qualitatively.

The present experiment gives data which enable a test to be made of whether this concept can explain results quantitatively, as well. Working back from values for response to total dose, the relative average "survival" from a single treatment dose was calculated from the results of applying this dose daily to 18 or to 25 days. A difference—small, as would be expected for this small difference in over-all time—is obtained from the two sets of data. Figure 3 shows that the effect of each treatment is not constant throughout the series, but becomes greater as the number of treatments increases. In other words, the dose effect is not repeated indefinitely. Any one of a number of possibilities, or combinations of them, may be the explanation. With repeated injury recovery may be incomplete, mitotic delay may be prolonged, and replacement may be less at the cell level. With a tumor *in vivo*, it seems probable that as the tumor shrinks during the treatment series, initially anoxic areas may improve their oxygen supply and become radiosensitive. This latter may be another advantage of protraction besides the differ-

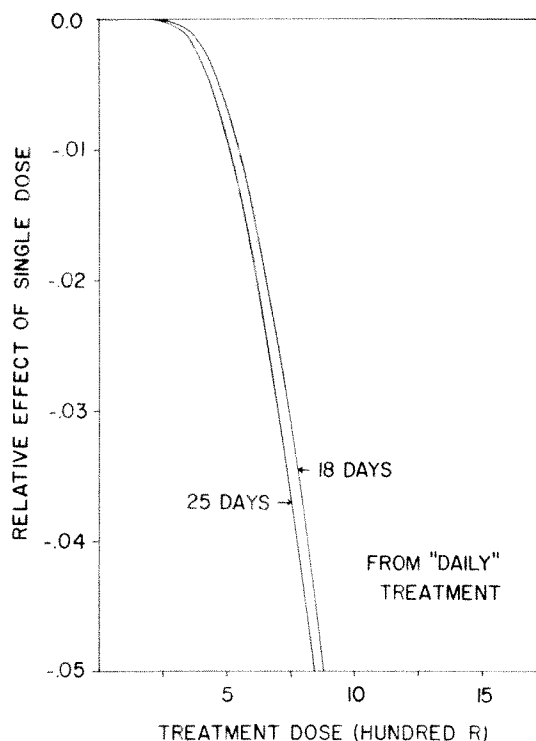


FIG. 3. Relative average "survival" of tumor for various single doses of radiation, calculated back from final cure rates. The average effect of each dose carried to 25 days is slightly greater than when carried to 18 days. This indicates that the lethal effect of each dose increases with repetition.

ence in slope of the time-dose lines for tumor and normal tissues.

When the data for treatment twice a week are examined, even greater differences in single dose effect are obtained, but again it seems best not to attempt a quantitative evaluation of this. This is consistent with the suggested oxygen-effect explanation since on the average the tumor size is smaller at each treatment time in this technique than for the same initial tumor size treated daily.

SUMMARY

Dose-response curves for cure of spontaneous mammary adenocarcinomas in C_3H mice by radiation maintain their slope for over-all times of 18 days and 25 days, and also for fractions given daily, three

times a week, and twice a week. Cure rates can be explained qualitatively in terms of treatment dose size, but quantitative examination shows that a given treatment dose becomes more effective with repetition. Among other possible explanations for this, the oxygen effect is suggested.

A possible optimum occurs for small treatment doses given three times a week.

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THE SECOND HALF-VALUE LAYER AND THE HOMOGENEITY COEFFICIENT*

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MILWAUKEE, WISCONSIN

IN HIS first papers describing the use of the half-value layer as a means of specifying "beam quality," Christen mentioned the use of the second half-value layer as a further means of describing the x-ray beam. He defined the second half-value layer as the absorber thickness required to reduce the dose rate from 50 per cent to 25 per cent of its initial value. In these same papers, Christen referred to the "index of heterogeneity" which he defined as the ratio of the second half-value layer to the first half-value layer.

In 1936, Thoraues¹⁸ proposed a method whereby the voltage and filtration would be adjusted to provide a spectrum having a specified band-width expressed in octaves. For most of the voltages and filters then in use the band-width would have been between 2 and 3 octaves.

Although the first half-value layer has been used for many years as the means of describing beam quality, the second half-value layer and Christen's idea of an index of heterogeneity seem to have received little attention. This was probably due to the fact that the practice of roentgen therapy evolved around a few selected kilovoltages and filters. Until the early 1930's roentgen therapy, in general, made use of three beam qualities often referred to as superficial, medium, and deep. The superficial quality usually called for the use of 100 kv. and filters of 0.5 to 2 or 3 mm. of aluminum. The medium quality beam was arrived at by using 135 to 140 kv. and a filter of 0.25 mm. copper plus 1.0 mm. aluminum. Deep therapy made use of 185 to 200 kv. and a filter of 0.5 mm. copper plus 1.0 mm. aluminum. The second half-value layer did not receive much attention,

for although Christen had in mind its use in roentgenography, the use of the first half-value layer was quickly lost in roentgenography but was applied to therapy. The filters that were used at the three voltages represented about as much filtration as could be used without reducing what was then called the beam intensity below a usable value. This was due to tube current limitations. As operating voltages and tube currents increased with improvements in roentgen-ray tubes and energizing equipment, there was some tendency to increase filtration in the deep therapy range but there was still no very great need for describing these beams by other than the first half-value layer. The result has been that the tables for depth dose, backscatter, etc., which the therapist has used have specified beam quality by means of the first half-value layer only.

In recent years, the increase in operating kilovoltage from 200 to 220, 250, and lately to 300 kv. may have brought about the need for specifying more than the first half-value layer. For example, 200 kv. peak with 0.5 mm. copper filtration will give a first half-value layer of approximately 1.0 mm. copper. A first half-value layer of 1.0 mm. copper can be obtained by using 300 kv. peak and 0.25 mm. copper. Although the first half-value layer for these beams is the same, there certainly is a difference in their spectral characteristics and to call attention to this fact, it would be necessary to document the kilovoltage or second half-value layer which would be quite different for the two conditions. The differences in these two beams could be described by stating the first and second half-value layer or could be described by

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the first half-value layer and something like Christen's "index of heterogeneity."

Taylor and Singer,¹⁷ in 1934, took cognizance of the need for additional information to describe the spectral distribution and advocated the use of the full attenuation curve. This is a very complete description of the beam but one not easily reproduced in papers, tables, etc. In 1959, the International Commission on Radiological Units and Measurements¹⁸ called attention to the matter and in its report discussed the more complete description of radiation quality by making use of both the first and second half-value layer. It defined the homogeneity coefficient as the ratio of the first to the second half-value layer and the heterogeneity coefficient as the reciprocal of the homogeneity coefficient. The homogeneity coefficient is unity for a monochromatic beam, but is always less than unity for a heterogeneous beam, the kind that is always used for roentgen therapy. In our laboratory, we thought it might be useful to explore the relation between the homogeneity coefficient and some common treatment factors; namely, backscatter factor and percentage depth dose. During this study we paid particular attention to the various mathematical methods that have been developed to compute spectral distribution since the accuracy of such spectra is directly related to the constants used to specify the beam quality. What follows is a result of these investigations. The first part of our study will concern the radiotherapist. While the matter of calculation of spectra may not be of direct interest to the radiotherapist, it will certainly be of interest to the radiation physicists and to those involved in the calibration of instruments.

EQUIPMENT AND INSTRUMENTATION

The roentgen-ray source used for these investigations was a resonant transformer operating at a nominal frequency of 1,200 cycles per second and using a grounded anode, beryllium window roentgen-ray tube. The equipment was capable of opera-

tion from 100 to 300 kv. peak at tube currents up to 20 ma. Both tube current and kilovoltage were electronically stabilized, providing excellent short and long time reproducibility of data. In addition, both the tube current and kilovoltage signals were monitored by DC potentiometers having 0.1 per cent accuracy and 0.05 per cent reproducibility.

Dose rate measurements were made using a Townsend balance system with a 0.1 per cent potentiometer as the readout element and a DC amplifier as the null detector. A 25-r Victoreen ionization chamber was employed with the above system for making half-value layer measurements at half-value layers greater than 2 mm. aluminum. This was supplemented by Victoreen low energy ionization chambers and a thin-window extrapolation chamber for the measurement of half-value layers less than 2 mm. aluminum.

HALF-VALUE LAYER AND HOMOGENEITY COEFFICIENT

In its simplest form, the determination of the first and second half-value layers consists of plotting an attenuation curve using narrow beam attenuation data and graphically determining the thickness of absorber necessary to reduce the dose rate from 100 per cent to 50 per cent and from 50 per cent to 25 per cent, *i.e.*, the first and second half-value layers. Figure 1 illustrates such a determination. In this case the first half-value layer is 0.65 mm. copper, the second half-value layer is 1.25 mm. copper, and the resulting homogeneity coefficient is 0.52. The abbreviations 1 HVL and 2 HVL will be used throughout this text to represent the first and second half-value layers, respectively.

First and second half-value layers were determined at 100, 140, 200, 250, and 300 kv. peak using filtration ranging from a minimum of 6 mm. of beryllium to a maximum of 8 mm. of copper. Figure 2 shows the first and second half-value layer plotted as a function of filter thickness for 200 kv. peak. It will be noted that the second half-

value layer is always higher than the first half-value layer and that the two converge with increasing filter thickness. Figures 3 and 4 show the first and second half-value layers, respectively, for the techniques employed in which copper filtration was used. The first and second half-value layers for the techniques employed in which aluminum filtration was used are shown in Figures 5 and 6, respectively. The measured value of the first half-value layer, second half-value layer, and the homogeneity coefficient for some typical combinations of kilovoltage and filtration are listed in Table 1.

Values of the homogeneity coefficient were calculated from the half-value layer data. A plot of homogeneity coefficient against first half-value layer for copper filtration is shown in Figure 7. The end points for the curves represent the half-value layer of the minimum wavelength radiation. The values of the first half-value layer, second half-value layer, and homo-

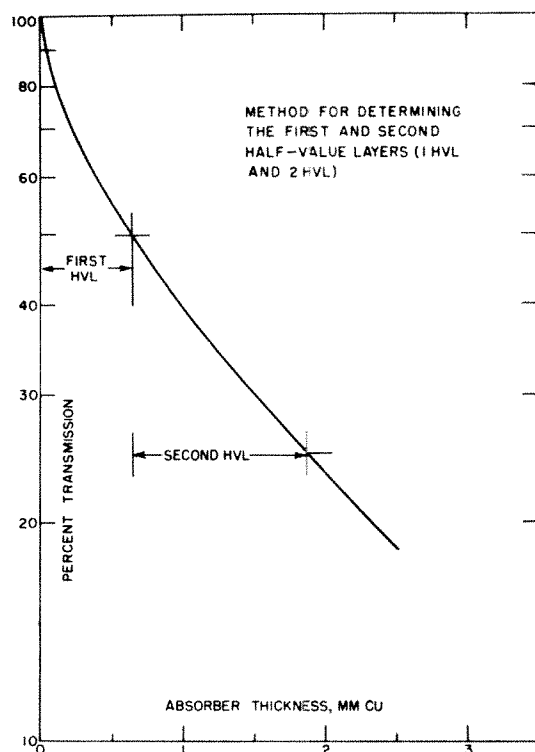


FIG. 1. Method for determining the first and second half-value layers.

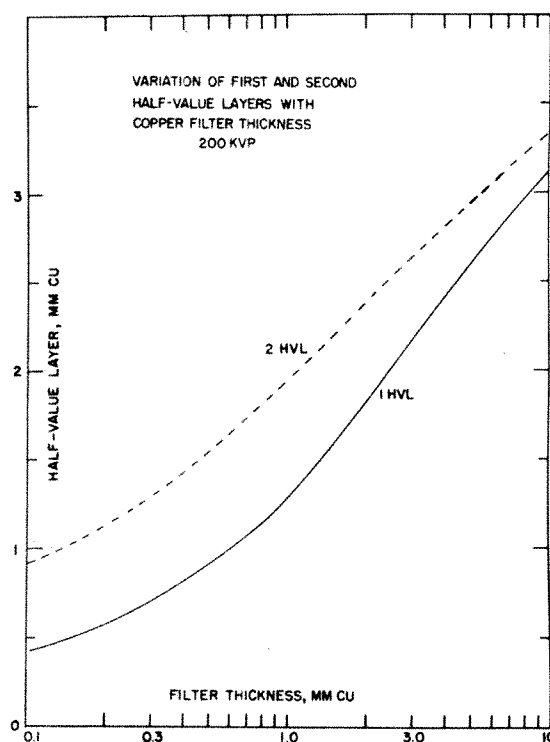


FIG. 2. Variation of first and second half-value layers with copper filter thickness (200 kvp.).

geneity coefficient were found to increase continuously as copper filtration was added at constant kilovoltage.

Homogeneity coefficients for aluminum filtration are shown in Figure 8. A minimum value of the homogeneity coefficient occurs at a first half-value layer of about 0.3 mm. aluminum. Zieler has shown that there is also a maximum value of the homogeneity coefficient which occurs at values of filtration and kilovoltage lower than those involved in these experiments and that these anomalies can be accounted for by assuming the presence of characteristic radiation in the roentgen-ray beam. The presence of these maxima and minima would seem to limit the practical application of the homogeneity coefficient to beams having a first half-value layer greater than about 0.3 mm. aluminum.

Using graphs relating kilovoltage, filtration, first half-value layer and homogeneity coefficient for a given roentgen-ray generator, it is possible to arrive at operating

TABLE I

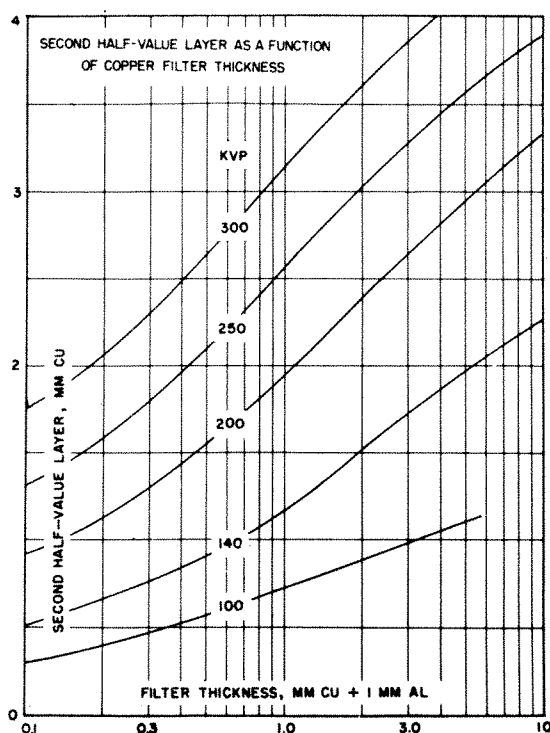
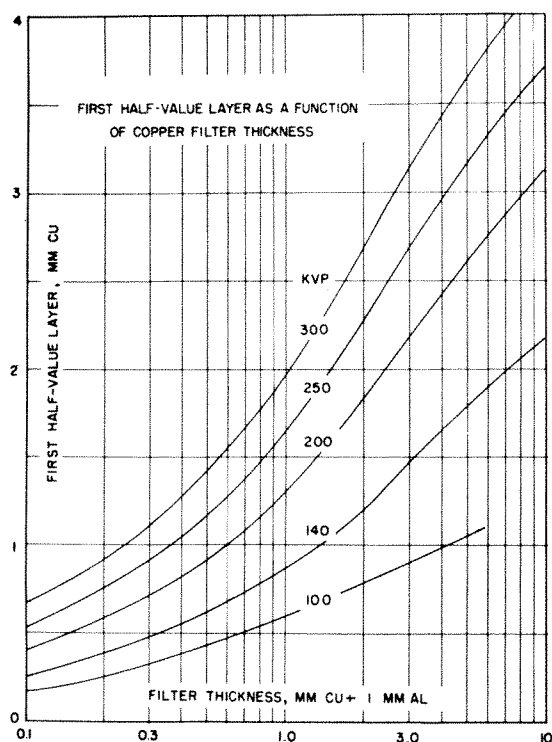
VALUE OF THE FIRST HALF-VALUE LAYER, THE SECOND HALF-VALUE LAYER, AND THE HOMOGENEITY COEFFICIENT FOR SOME TYPICAL TREATMENT TECHNIQUES

Kv. Peak	Filter	1 HVL	2 HVL	Homogeneity Coefficient
100	1.0 mm. Al	1.50 mm. Al	2.91 mm. Al	.52
100	3.0 mm. Al	3.24 mm. Al	4.96 mm. Al	.65
140	0.25 mm. Cu, 1 mm. Al	0.428 mm. Cu	0.728 mm. Cu	.59
200	0.5 mm. Cu, 1 mm. Al	0.920 mm. Cu	1.545 mm. Cu	.60
200	1.0 mm. Cu, 1 mm. Al	1.291 mm. Cu	1.93 mm. Cu	.67
250	0.5 mm. Cu, 1 mm. Al	1.163 mm. Cu	2.10 mm. Cu	.56
250	1.0 mm. Cu, 1 mm. Al	1.637 mm. Cu	2.55 mm. Cu	.64
250	3.0 mm. Cu, 1 mm. Al	2.690 mm. Cu	3.28 mm. Cu	.82
300	1.0 mm. Cu, 1 mm. Al	1.967 mm. Cu	3.12 mm. Cu	.63
300	2.0 mm. Cu, 1 mm. Al	2.710 mm. Cu	3.60 mm. Cu	.75
300	4.0 mm. Cu, 1 mm. Al	3.440 mm. Cu	4.00 mm. Cu	.86

techniques yielding the same first half-value layer and homogeneity coefficient for different types of equipment. It is possible, for instance, to obtain a first half-value layer of 0.4 mm. copper and a homogeneity coefficient of 0.6 on both constant poten-

tial generators and self-rectifying equipment by selection of kilovoltage and filtration.

Table II shows some combinations of kilovoltage and filtration which yield the same first half-value layer and homogeneity



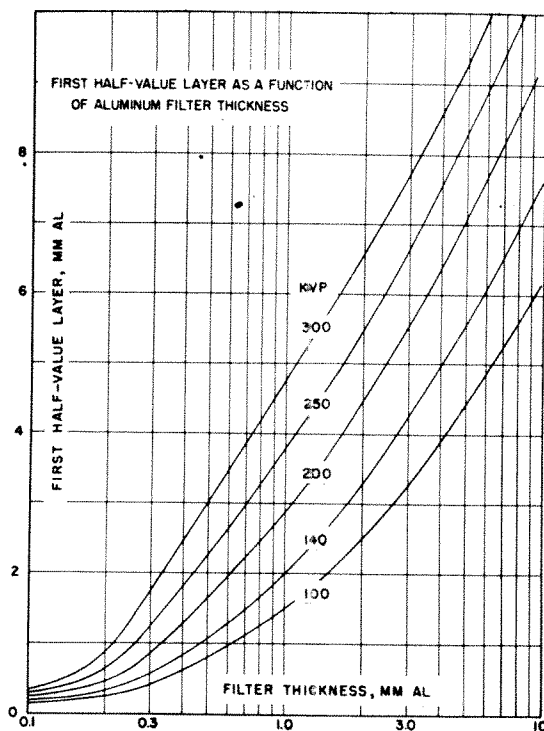


FIG. 5. First half-value layer as a function of aluminum filter thickness.

coefficient for constant potential and pulsating equipment. The 120 kv. point is taken from data by Taylor and Singer¹⁷ and the 250 kv. point is taken from data by Somerwil.¹⁶ Pulsating data are derived from those presented above.

POSSIBLE ERRORS IN DOSAGE

The principal shortcoming, if there is one, of the first half-value layer as the sole

TABLE II

COMPARISON OF OPERATING TECHNIQUES WHICH YIELD THE SAME FIRST HALF-VALUE LAYER AND HOMOGENEITY COEFFICIENT

Generator	1 HVL (mm. Cu)	Homogeneity Coefficient	Kv. Peak	Total Filter (mm. Cu)
Pulsating	0.4	0.6	130	0.28
Constant				
Potential	0.4	0.6	120	0.34
Pulsating	2.56	0.76	274	2.15
Constant				
Potential	2.56	0.76	250	2.00

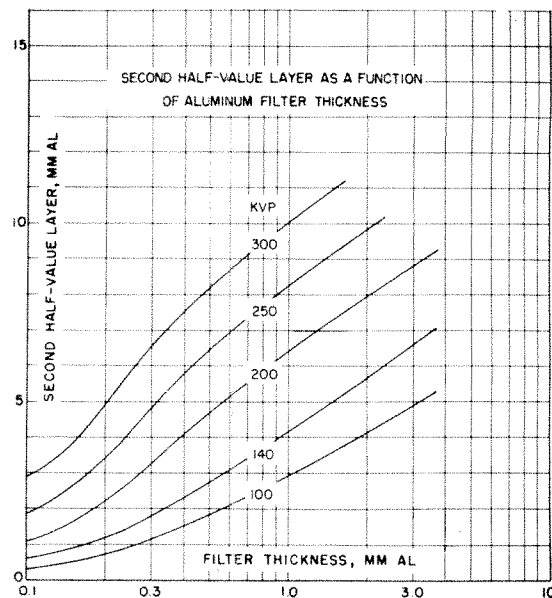


FIG. 6. Second half-value layer as a function of aluminum filter thickness.

measure of radiation quality would seem to be its inability to uniquely define the distribution of radiation within a treatment volume. Backscatter factor and per cent depth dose were therefore measured for many combinations of kilovoltage and filtration and the values obtained at a given first half-value layer were compared to determine what errors could possibly be incurred.

Backscatter factors were measured using a field 10×10 cm. square at a distance of 50 cm. from the focal spot. Mix D was used

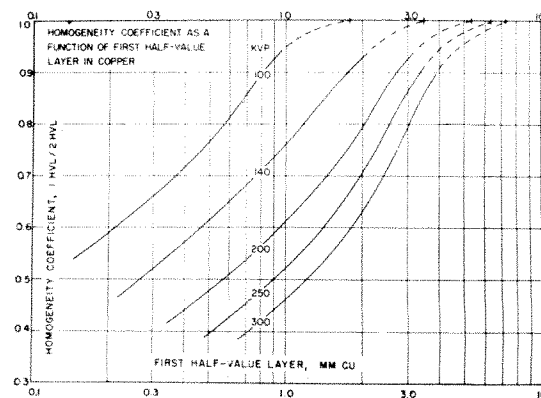


FIG. 7. Homogeneity coefficient as a function of first half-value layer in copper.

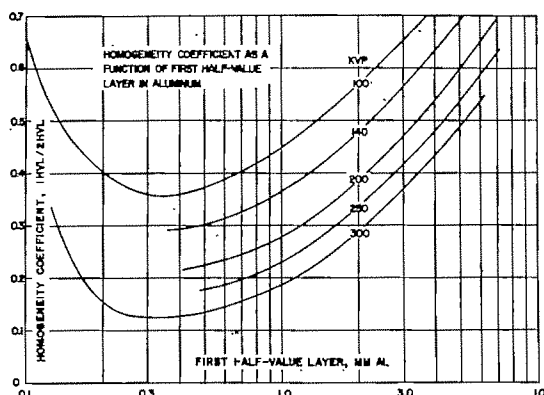


FIG. 8. Homogeneity coefficient as a function of first half-value layer in aluminum.

as the scattering material and the measurements were made using a thin wall ionization chamber and preamplifier previously described. The backscatter factor was measured at 100, 140, 200, 250, and 300 kv. peak, using filters ranging from the inherent filtration of 6 mm. beryllium to 8 mm. copper. The backscatter factors are shown plotted as a function of first half-value layer at each of the kilovoltages in Figure 9. Measurable differences were present at most radiation qualities with the greatest differences existing in the region around a first half-value layer of 1 mm. copper. In general, a higher backscatter factor results when a given first half-value layer is produced at a lower kilovoltage, or a higher homogeneity coefficient. This is not true, however, at the lower first half-

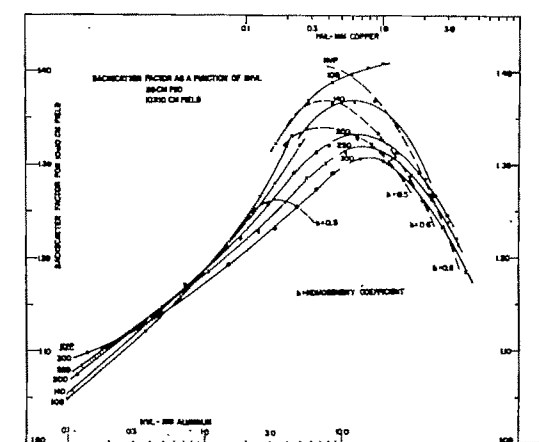


FIG. 9. Backscatter factor as a function of 1 HVL.

TABLE III
TECHNIQUES USED TO OBTAIN A HALF-VALUE
LAYER OF 1.0 MM. CU

Kv. Peak	Filter	Homogeneity Coefficient
140	1.35 mm. Cu, 1 mm. Al	.77
200	0.60 mm. Cu, 1 mm. Al	.61
250	0.36 mm. Cu, 1 mm. Al	.52
300	0.235 mm. Cu, 1 mm. Al	.46

value layer where the reverse tends to be true.

The depth dose near the surface of the phantom was investigated using a water phantom since very thin and uniform thicknesses of Mix D proved difficult to fabricate. Using a 10×10 cm. square field at 50 cm. from the focal spot, the depth dose was measured to a depth of 2 cm. for a first half-value layer of 1 mm. copper. The first half-value layer of 1 mm. copper was obtained at the combinations of kilovoltage and filtration shown in Table III.

Figure 10 shows the percentage depth dose plotted as a function of depth for each of the above techniques. The total difference in depth dose for the rather wide range of kilovoltages is only about 2 per cent when referred to the surface dose. The error in calculated depth dose becomes somewhat greater, however, when the backscatter factors of Figure 9 are used to determine the depth dose as a function of the air dose. Figure 11 shows a plot of depth dose per roentgen in air. While the extent to which the half-value layer fails to unambiguously define the depth dose as a result of changes in backscatter may be significant, the extremes of kilovoltage and filtration used in this study are rarely used in practice.

In order to assess the uniqueness with which the per cent depth dose is defined by the first half-value layer at greater depths, the per cent depth dose was measured at a single depth for a field 10×10 cm. square at a 50 cm. distance. Figure 12 shows the percentage depth dose at a depth of 10 cm. for several kilovoltages using aluminum

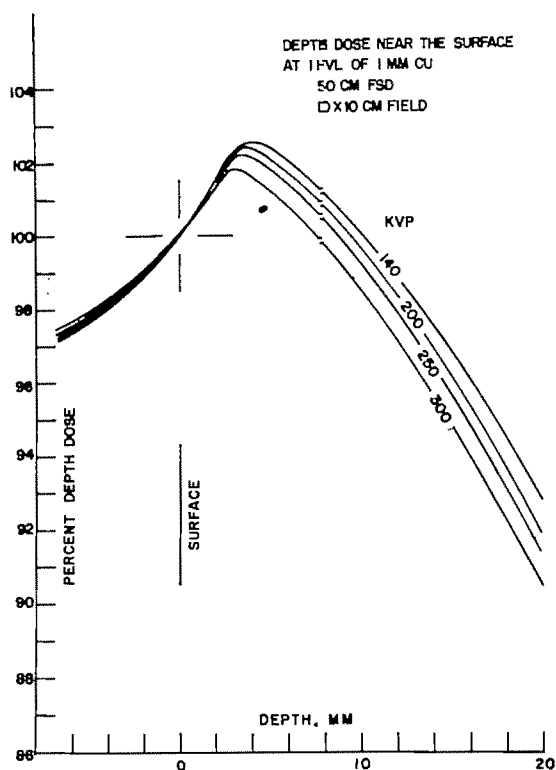


FIG. 10. Depth dose near the surface at 1 HVL of 1 mm. Cu.

filters ranging in thickness from 0 to 8 mm. to obtain first half-value layers from 0.1 to 9.2 mm. aluminum. The depth doses for the higher kilovoltages were higher throughout most of the range investigated, with the data converging to a negligible difference at a half-value layer of about 5 mm. aluminum. Figure 13 shows a similar plot for copper filters. Differences in the per cent depth dose were small throughout most of the range with some divergence of data at a minimum filtration of 0.235 mm. copper plus 1 mm. aluminum.

ABSORPTION ANALYSIS SPECTROMETRY

In addition to its use as a means of specifying the treatment technique for the clinician, the half-value layer has some absolute significance to the physicist who may be interested in the spectral distribution of the radiation. The mathematical process of absorption analysis originated by Silberstein in 1933 was constantly im-

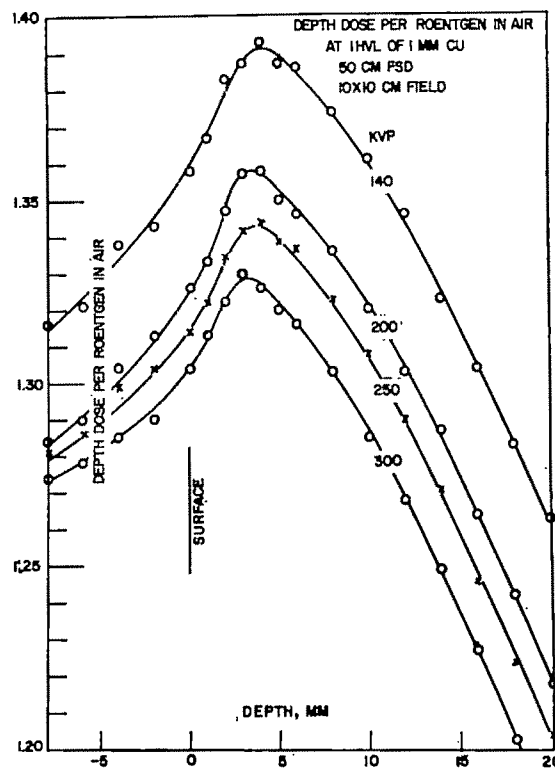


FIG. 11. Depth dose per roentgen in air at 1 HVL of 1 mm. Cu.

proved upon since it is based upon the fact that a precisely measured attenuation curve infers one and only one spectrum. The process of determining that spectrum is not an easy one and, in general, the accuracy with which it is done depends upon the amount of good absorption data available and the amount of time spent in perform-

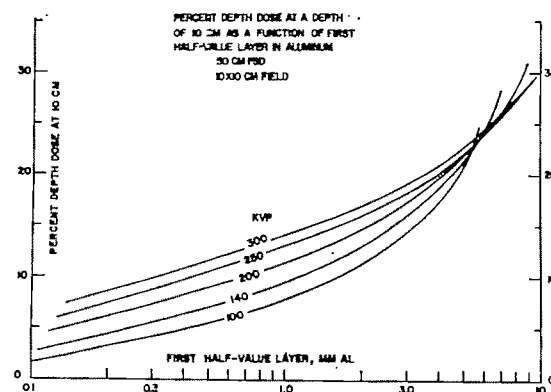


FIG. 12. Per cent depth dose at a depth of 10 cm. as a function of first half-value layer in aluminum.

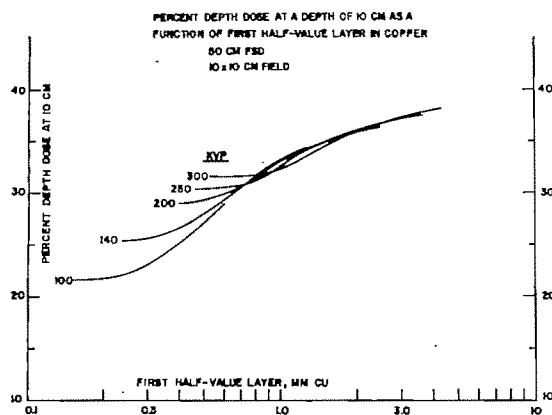


FIG. 13. Per cent depth dose at a depth of 10 cm. as a function of first half-value layer in copper.

ing the analysis. Historically, the process has developed from a simple one involving a small number of undetermined constants to a more complex one involving a large number of undetermined constants. The requirements placed on the absorption data have likewise progressed from a small number of points to a large number of points. The absorption data required by the techniques of several workers are shown in Table IV. The methods are arranged in order of increasing complexity and accuracy.

Several spectra have been plotted using the three simplest methods listed in Table IV. Figure 14 shows spectra plotted for comparison by the three methods for 140 kv. peak, first half-value layer 0.5 mm. copper. The amount of characteristic radiation re-

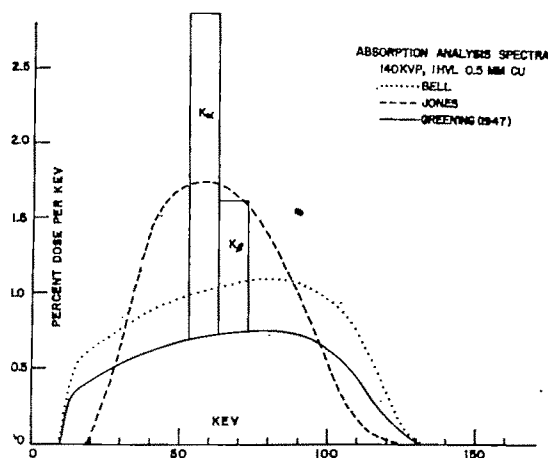


FIG. 14. Absorption analysis spectra, 140 kVp., 1 HVL 0.5 mm. Cu.

sulting from the Greening⁶ (1947) method is plotted as an area proportional to its contribution for comparison purposes. Figures 15, 16, and 17 show plots using the same methods for 200, 250, and 300 kv. peak. These spectra should not be taken as the limit of accuracy of the absorption analysis technique but are shown merely to illustrate what can be derived from a small amount of absorption data.

A test of the accuracy of such a spectrum is a comparison of the absorption curve derived from the spectrum with the experimental absorption curve. Such a comparison is shown in Figure 18 for 140 kv. peak. The more complex methods are observed to provide progressively better fit to the ex-

TABLE IV

SUMMARY OF MINIMUM DATA REQUIRED FOR SOME ABSORPTION ANALYSIS SPECTRA

Method	Minimum Data Required
Bell ²	First half-value layer and kv. peak
Jones ⁹	First and second half-value layer and kv. peak
Greening ⁶ (1947)	Four or more points on the attenuation curve and kv. peak
Emigh and Megill ⁴	Many points on the attenuation curve and kv. peak
Greening ⁷ (1950)	Many points on the attenuation curve and kv. peak

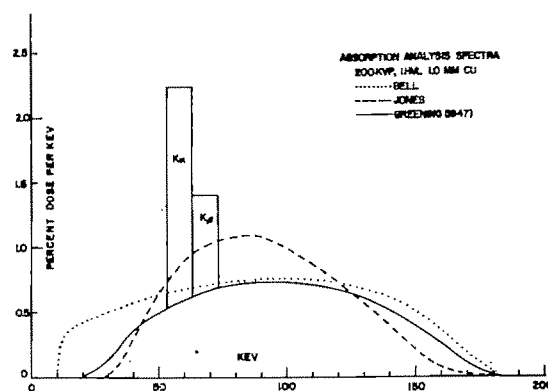


FIG. 15. Absorption analysis spectra, 200 kVp., 1 HVL 1.0 mm. Cu.

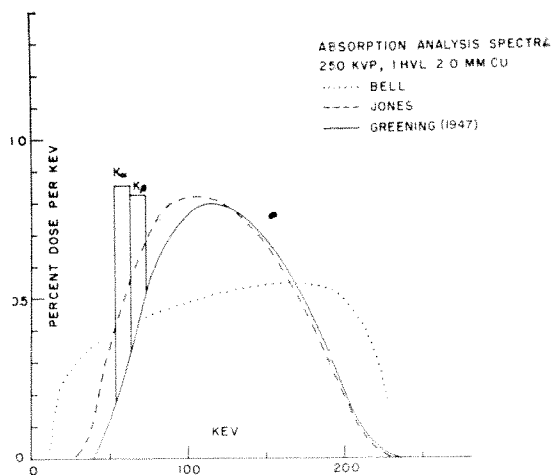


FIG. 16. Absorption analysis spectra, 250 kvp., 1 HVL 2.0 mm. Cu.

perimental absorption curve and hence represent the actual spectrum more accurately. It is interesting to compare the spectrum so derived to one derived by another method. Figure 19 shows a comparison of a 140 kV. peak spectrum derived from our data by a more complex method (Greening,⁷ 1950) to a spectrum from a constant potential generator measured by Hettinger and Starfelt⁸ using scintillation spectrometry. Both spectra represent beams having the same first half-value layer, 0.5 mm. copper. The Hettinger and Starfelt⁸ spectrum was converted from a photon spectrum to a dose

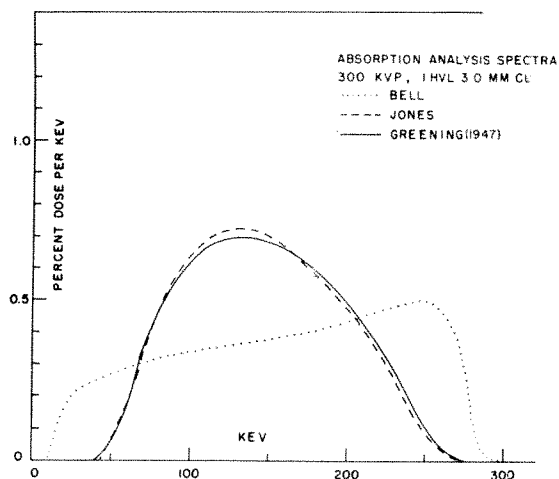


FIG. 17. Absorption analysis spectra, 300 kvp., 1 HVL 3.0 mm. Cu.

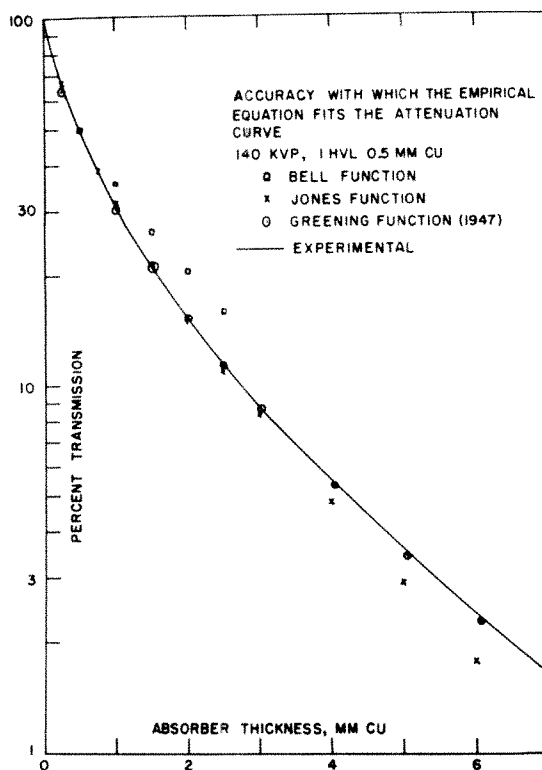


FIG. 18. Accuracy with which the empirical equation fits the attenuation curve.

spectrum and attenuated to a first half-value layer of 0.5 mm. copper. While the difference in waveform would be expected to produce some differences, the agreement of the two spectra may be well within the limits necessary to many calculations.

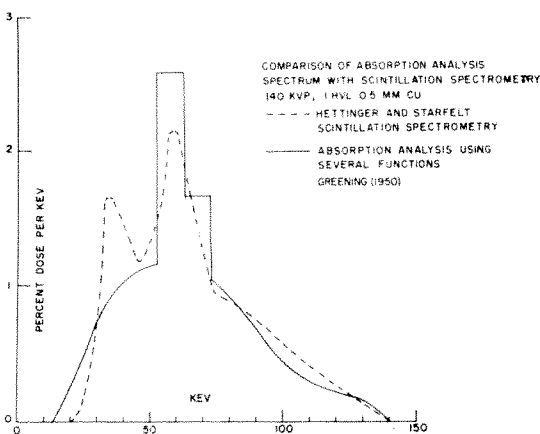


FIG. 19. Comparison of absorption analysis spectrum with scintillation spectrometry.

DETERMINATION OF INHERENT FILTRATION AND KILOVOLTAGE

A knowledge of the first half-value layer has been used as a means of estimating kilovoltage and filtration. For instance, knowing the kilovoltage, waveform, and first half-value layer, one can determine the inherent filtration by referring to plots of first half-value layer against filtration at known kilovoltages made on equipment having the same waveform. Conversely, knowing the inherent filtration, waveform, and half-value layer, one can determine the kilovoltage at constant filtration.

A knowledge of the first and second half-value layers for a given operating condition can be used to determine kilovoltage and filtration with some confidence, provided graphs showing the first and second half-value layer as a function of filtration and kilovoltage peak are available for equipment having the same waveform. For practical purposes graphs for only sine wave and constant potential equipment would seem to be necessary for the determination of filtration and kilovoltage.

The actual determination of the kilovoltage and filtration may be done by determining the intersection of two graphs, one of kilovoltage against filtration at constant first half-value layer and one of kilovoltage against filtration at constant homogeneity coefficient. Such a determination is shown in Figure 20 for a first half-value layer of 1.75 mm. aluminum and a homogeneity coefficient of 0.5. The plot of kilovoltage against filtration at a constant first half-value layer is taken from the intersections of the line in Figure 5 representing a first half-value layer of 1.75 mm. aluminum with the lines representing the various kilovoltages. The plot of kilovoltage against filtration at a constant value of the homogeneity coefficient is taken from the intersections of the line in Figure 8 representing a homogeneity coefficient of 0.5 with the lines representing the various kilovoltages. Since Figure 8 shows homogeneity coefficient plotted against first half-value layer, it is necessary

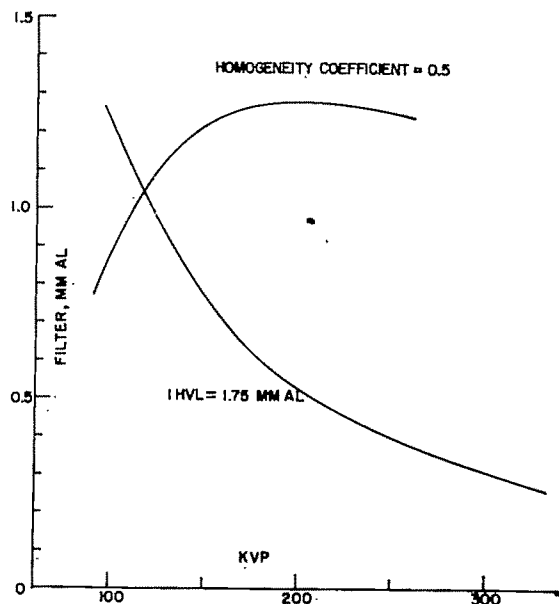


FIG. 20. Kilovolts (peak) and filtration from measured first and second half-value layers and known absorption data.

to determine the corresponding filtration from Figure 5. The resulting intersection of the two lines in Figure 20 occurs at a filtration of 1.05 mm. aluminum and a kilovoltage of 117 kv. peak. The knowledge of the first and second half-value layers has hence allowed the determination of both kilovoltage and filtration rather than one or the other as would be the case where only the first half-value layer was known.

SUMMARY

From our work we would conclude:

1. The first half-value layer alone does not completely describe the "quality" or spectral distribution of a roentgen-ray beam.
2. A better description would result from stating both kilovoltage peak and the first half-value layer.
3. A still more complete description can be had by a statement of the first and second half-value layers or by a statement of the first half-value layer and the homogeneity coefficient.
4. The most comprehensive description,

as was pointed out by Taylor and Singer,¹⁷ is a presentation of a complete absorption curve, but this involves space considerations not always feasible.

5. The first half-value layer does not uniquely define the depth dose, but the degree to which it fails to do so may be negligible for clinical purposes.

6. A knowledge of the first and second half-value layers may be used to estimate kilovoltage peak and filtration.

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DOSIMETRY BY TOMOGRAPHY IN INTERSTITIAL CURIETHERAPY: POINT TECHNIQUE*

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THE calculation of the spatial dose delivered to the tissues during interstitial curiethery has presented difficult problems which arise, on one hand, from the fact that the radiating sources are imbedded in the tissues—making any direct measurements an impractical task—and, on the other hand, from the unequal distribution of the dose around these sources in the tumor.

Several methods have been devised in which indirect or semi-direct spatial reconstructions of the implants are made.^{1,3,5} These methods do not establish the isodose pattern of the implant and do not show the neighboring structures which occasionally receive considerable doses of radiation—fundamental conditions for good dosimetry.

Patients treated with curiethery at the Institut Gustave-Roussy have tomograms taken, through a plane perpendicular to the long axis of the implant, besides the usual frontal and lateral roentgenograms. It is with the help of these tomograms and the isodose curves of the radioactive material used, that it is possible to calculate with great accuracy the spatial dose delivered by the implant during treatment.

PRINCIPLE OF THE METHOD

The method is used mainly in those implants in which the needles or wires of any solid, uninterrupted radioactive material follow parallel lines.

The images of the needles or wires will appear on the tomogram as points (Fig. 1). These are marked on tracing paper and on each point (corresponding to a source) the center of a standard circular isodose chart, enlarged to compensate for the enlarge-

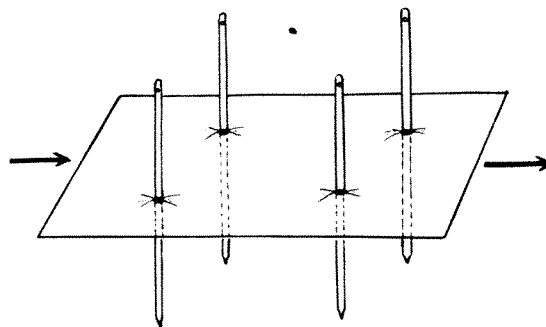


FIG. 1. Tomographic dosimetry, the "point technique." The plane of the unidirectional tomogram sections perpendicularly 4 radium needles which appear on the film as 4 points.

ment on the film, is placed and the isodose curves around the source are drawn.

By adding the values of the superimposed isodose curves at each point, it is possible to calculate the isodoses for the entire implant and to determine the dose in the tumor and surrounding structures (point technique).

TECHNIQUE OF TOMOGRAPHY

The technique of tomography will depend upon the orientation of the radioactive sources.

A. VERTICAL IMPLANTS

If the radioactive sources are oriented in a vertical fashion or closely approximating it, we advise the use of an axial transverse tomogram. The image so obtained is that of a transverse section of the body at the level of the implant.^{2,6} An example of such an implant is shown in Figure 2. This roentgenogram was taken of a patient with a squamous cell carcinoma of the right tonsillar region in which a double wire of radioactive gold 198 was inserted into the

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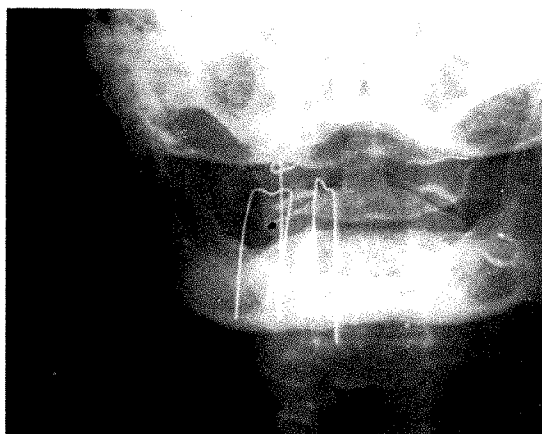


FIG. 2. Carcinoma of the right tonsillo-lingual region: 2 double plus 1 single wire of Au^{198} implanted. Frontal roentgenogram.

tonsillar region and another double wire and a single wire of the same material were implanted in the adjacent area of the tongue.⁷ The appearance of the implant is that of a cylinder with a 4 cm. vertical axis.

(a) *Projection of the axis of the implant on the skin.* Immediately after the implantation of the radioactive sources, the position of the implant is determined by fluoroscopy or still better with the aid of frontal and lateral roentgenograms. The projection of the vertical axis of the implant on the skin is marked with a dermatographic pencil. A line perpendicular to this axis of implant is also marked on the skin at a level which corresponds to the center of the irradiated volume of tissue. It is at this level that the tomographic section of the region will be made (Fig. 3A).

(b) *Positioning of the patient in the tomographic unit.* The patient is placed in a sitting position on the tomographic chair and is conveniently immobilized. The main axis of the implant, as shown by its cutaneous projection mark, is put in coincidence or parallelism with the rotational axis of the chair with the aid of a Trope centralizing light. The horizontal line already drawn on the skin is made to coincide with the horizontal light beam, and it will establish the plane of body section for the tomogram (Fig. 3B).

(c) *Distance and exposure factors.* The incident roentgen beam is angulated 20 de-

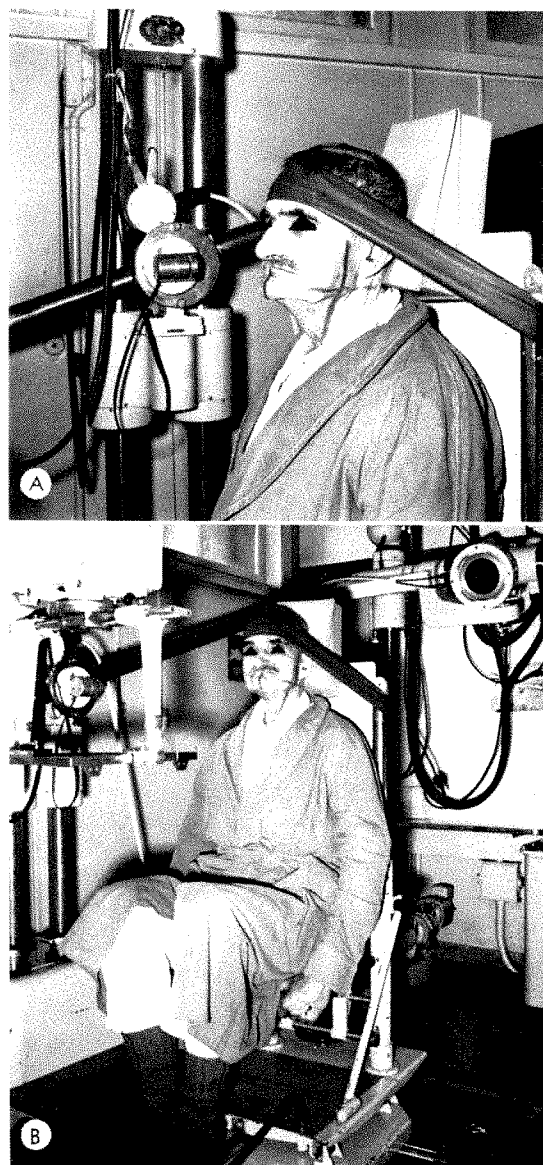


FIG. 3. (A and B) Carcinoma of the tonsillo-lingual region. The patient is positioned for tomography. The vertical lines on his face correspond to the projection of the principal axis of implant of the Au^{198} wires; the horizontal line corresponds to the level of section of the transverse tomogram.

grees up from the horizontal. A distance of 180 cm. from the focus to the axis of rotation of the seat and a distance of 60 cm. from this seat-rotation axis to the axis of rotation of the cassette are used. This gives an enlargement coefficient of 1.33. We employ 80 kv., 40 ma. and an exposure of 4 seconds during which time the patient is completely rotated.

(d) *Reading of the film.* The tomogram will show the cutaneous contour and the different anatomic structures corresponding to the section of the body under study. The radioactive sources will appear in the form of points as already mentioned. In Figure 4 we are able to recognize the 5 points that correspond to the transverse section of the radioactive wires (2 double and one single wire of gold 198). The skin contour, the body of the mandible, the tongue, the cervical column, etc. and their relation to the implant are readily visualized. A tracing for calculation of the isodoses is easily done.

B. HORIZONTAL (FRONTAL, OBLIQUE, OR SAGITTAL) IMPLANTS

If the implantation is done in a horizontal plane, unidirectional tomography is used according to the position of the implant plane (by following Grossmann's recommendations).⁸

The technique employed for the projection of the implant on the skin and the positioning of the patient in the tomographic chair are identical to those described for transverse tomography, except for change of the cutaneous planes and a corresponding change of the light localizing device. The focus-seat-cassette distances remain the same and the enlargement coefficient will also be the same, namely 1.33 (Pantomix CGR). For example, in a patient who has a sagittal implant of 4 wires of iridium 192 for cervical lymph node metastases (2 central wires 8 cm. long and 2 marginal wires 6 cm. long) the tomogram is taken in a frontal plane using the following factors: a sweeping angle of 50 degrees, 70 kv., 40 ma., and an exposure (and moving) time of 2 seconds.

The film yields information comparable to that obtained in transverse tomography. The tomographic images of the radioactive sources will show fading tails around their own transverse sections ("butterfly knots") (Fig. 5 and 6).

CALCULATION OF THE ISODOSES

A tracing of the tomogram is made on transparent paper by ensuring the proper relationship of the cross section of the radioactive sources to the anatomic structures.



FIG. 4. Carcinoma of the right tonsillo-lingual region. Implantation of 5 parallel Au¹⁹⁸ wires, 4 cm. long. On the transverse tomogram the images of the sectioned wires appear as 5 points.

The radiotherapist must have a complete set of standard isodose curves in a plane perpendicular to the axis of the radioactive implant. The isodose curves represent circular lines around the cross section of the sources constituting the implant. Different sets are necessary for different lengths (2, 4, 6, 8, 10, 12 cm.) and for different radioactive materials. They should be calculated in roentgens/hour per 1 mc/cm. (Fig. 7 and 8). These curves are magnified by a factor of 1.33 (the same as the enlargement coefficient of the film) so that they can be used directly on the tracing of the tomogram.

The center of the standard isodose curves, corresponding to the length and material used in the implant, is placed on the point of the tomogram representing the cross section of that source. The different isodose curves are superimposed on the tracing paper using different colors to facilitate their identification (Fig. 9 and 10).

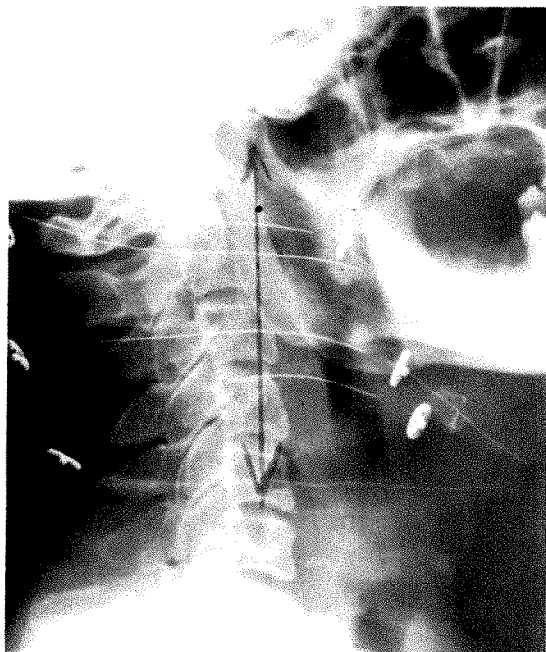


FIG. 5. Right cervical lymph node metastases. Four Ir^{192} wires (2 central 8 cm. and 2 marginal 6 cm. in length). Lateral roentgenogram.

By adding the values of the proper isodose curves for each source or point, finally the



FIG. 6. Right cervical lymph node metastases. Four Ir^{192} wires inserted. Unidirectional frontal tomogram. The 4 wires appear on the film as 4 points with tails as "butterfly knots."

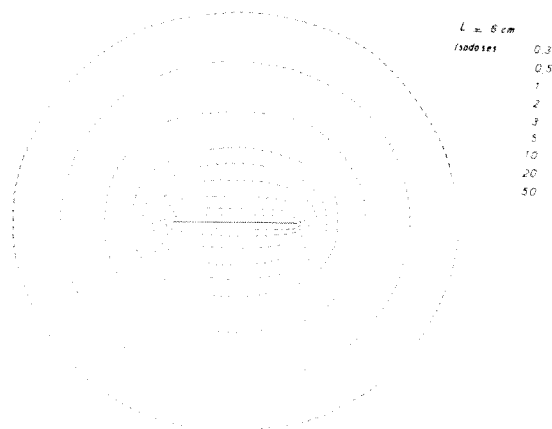
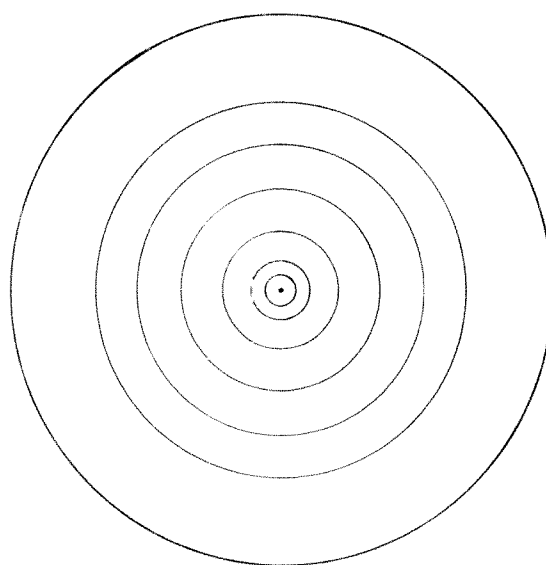


FIG. 7. Calculated isodose curves around the main axis of a 6 cm. long Ir^{192} wire (1 mc/cm. activity; dose in r/hr.).

isodose curves that correspond to the entire implant considered as a unit are obtained. First the calculation of the dose at the center of the implant is made, then the position and value of the first isodose line that will encircle the implant as a whole are determined. This represents the *basic isodose curve* of the implant.



Isodoses 1, 2, 3, 5, 10, 20, 50

FIG. 8. Calculated isodose curves in a plane perpendicular to the center of the Ir^{192} wire indicate the circular isodose curves that will be used in our point dosimetry (1 mc/cm. activity; 6 cm. length; dose in r/hr.).

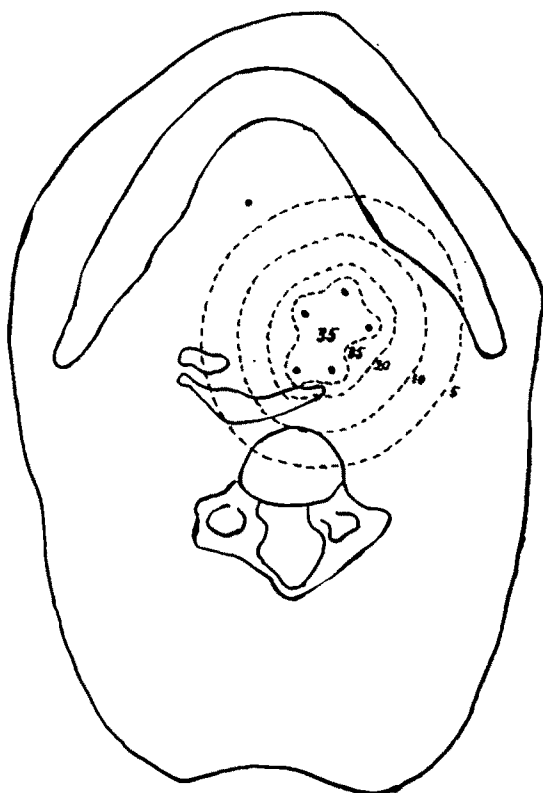


FIG. 11. Right tonsillo-lingual carcinoma. Au^{198} implant consisting of 2 double and 1 single wire 4 cm. long. Transverse tomogram. The calculated isodose curves drawn around the implant show decreasing numerical values distally from the implant. The surrounding anatomic structures are also shown (dose in r/hr.).

which the irradiating sources are located. The isodoses are determined on an anatomic and topographic basis, including the tumor plus the surrounding normal tissues. Dosage can be controlled and calculated in any region of the tumor and its vicinity.

2. In the tomographic study of the tumor and its surrounding structures, one can easily differentiate between bone, air and soft tissue, although differentiation between various components of soft tissue structures is more uncertain. This can be determined by careful observation of the topography of the organs and their relations, or by the use of radiopaque materials in the soft tissues one wishes to delineate. The latter procedure, however, will intro-

duce shadows into the tomogram that might be confused with the radioactive sources.

3. The method herein described has its principal application in the parallel and non-interrupted implants, the isodose curves of which can be calculated at any level. It is also relatively useful in other types of implants such as:

(a) In the case of gold 198 double wire in which it is necessary to take into account the amount of irradiation given by the horizontal branch of the wire for the calculation of the total dose. This correction can easily be made by adding the extra dose to the standard isodoses in the main plane of the double wire.⁷

(b) In the case of curved lines, the correction is more difficult; the arch of curvature should be taken into consideration and, for the correction, special graphs or tables must be consulted.⁴

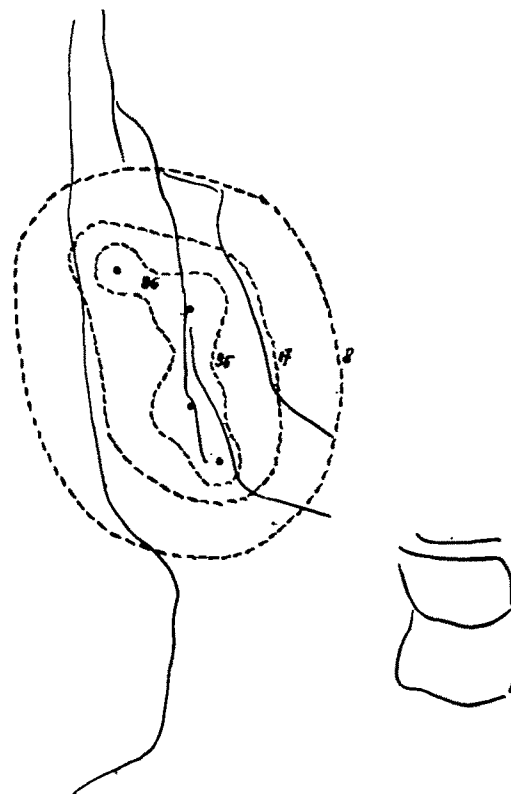


FIG. 12. Right cervical lymph node metastases. Ir^{192} implant consisting of 2 wires 6 cm. and 2 wires 8 cm. long. Frontal tomogram (dose in r/hr.).

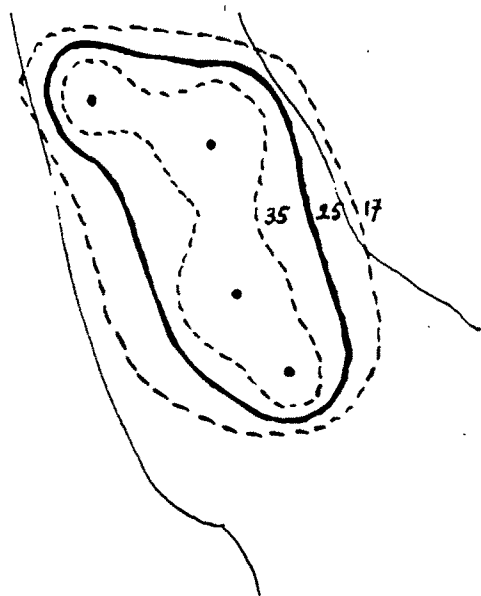


FIG. 13. Right cervical lymph node metastases. The volume to be irradiated is drawn in a thick line at some distance from the basic isodose curve. In this case, the basic isodose curve with a value of 35 does not correspond to the reference isodose curve of the volume to be irradiated which has a value of 25. The tumor dose will be calculated from the isodose curve 25, with the knowledge that there will be a central overdosage. As an example, if the chosen tumor dose is 5,000 rads, the central zone of the volume to be irradiated, at the level of the basic isodose curve, will receive 7,000 rads.

(c) In the case of loop implants, they can be arbitrarily considered as rectangular implants, resembling the gold 198 double wire with a horizontal branch (Fig. 14).

(d) In the rare cases of implants in spiral fashion, the dosimetric problem is even more complex. Tomograms can be helpful provided the section crosses the main plane of the cylinder or ovoid formed by the spiral.

4. High density wires can easily be detected in the tomographic section of the body in which they are implanted. We have made tomograms using aluminum, steel, iridium-platinum, and lead wires with a diameter of 0.3 mm. imbedded in phantoms of wax and water. In a 30 cm. diameter cylinder (corresponding to the pelvic dimensions) the iridium-platinum and lead wires were the only ones clearly visualized in the film.

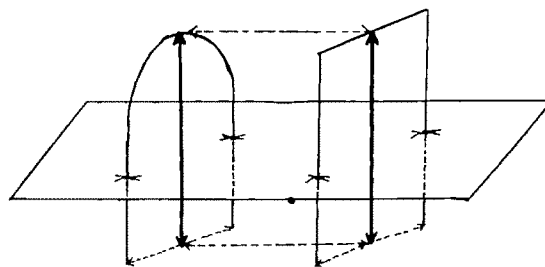


FIG. 14. Schematic drawing illustrating conversion of a loop into a rectangular form.

5. Parallel insertion of the radioactive sources is a necessary condition for any correct tomographic dosage. This parallelism may not be achieved on occasions due to technical or anatomic difficulties. In such cases an angulation of the sources that does not exceed ± 10 degrees will produce on the basic isodose curve a negligible variation in dosimetry. For inclinations of a greater degree, it is necessary to make a correction (Fig. 15). On the other hand, it is necessary in these unparallel implants to control the dose by taking several tomograms at different levels.

SUMMARY

The use of tomography in interstitial curietherapy allows a direct dosimetry in which a spatial representation of the isodoses in the tumor and in the surrounding normal structures can be made.

The tomogram is taken in a plane perpendicular to the implant axis. The images of the needles or wires of the radioactive sources implanted will be seen as points and upon these points the standard isodose curves are drawn and added for the calculation of the dose delivered to the tumor and the surrounding structures.

This method is simple, particularly suitable for implants in which the sources are linear and are inserted parallel to one another.

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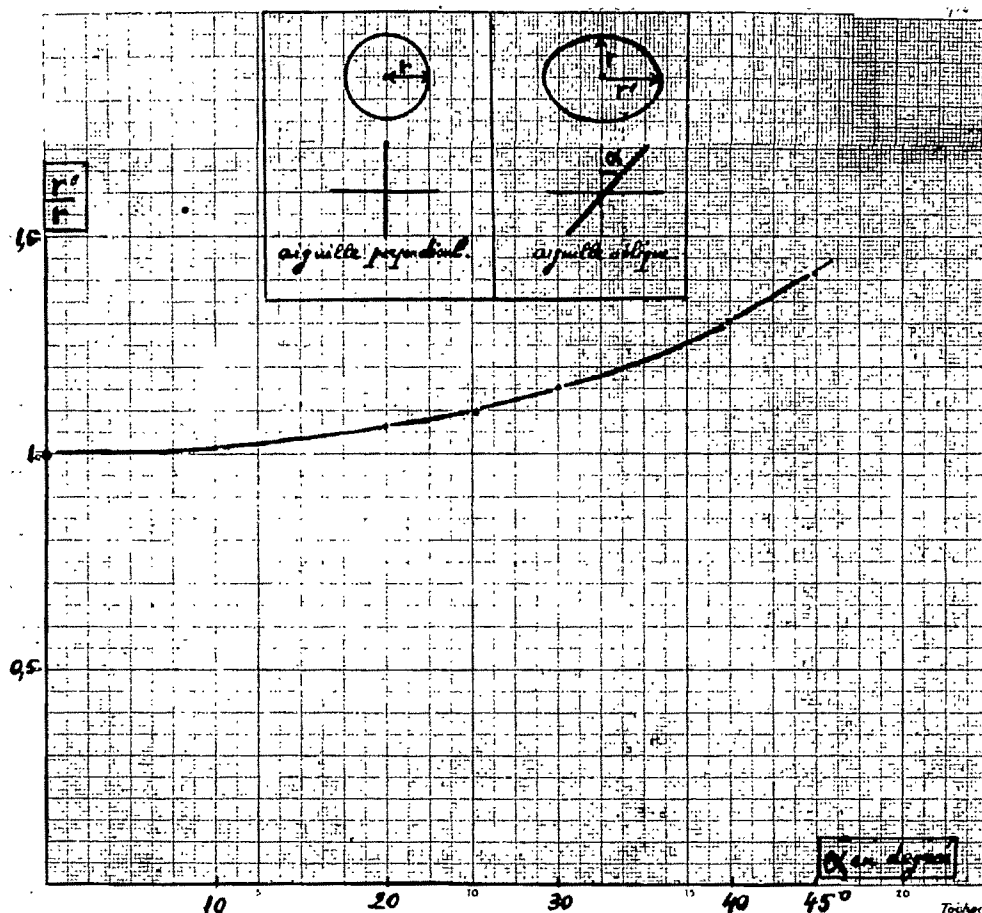


FIG. 15. Graph for correction of isodoses in case that the radioactive wires or needles are not placed parallel to each other.

ACKNOWLEDGMENT

We wish to express our appreciation to Madame A. Dutreix, Ph.D., for her advice and technical aid.

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WORLD SURVEY OF RADIOISOTOPE TELETHERAPY UNITS*

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IN THE ten years time since the first 2 cobalt 60 teletherapy units were installed in 1951 in Canada, radioisotope teletherapy has come to be widely accepted in the treatment of certain types of cancer. The number of units in use has grown rapidly. Besides cobalt 60, cesium 137 is also used as a teletherapy source, and there is also one iridium 192 unit in existence.*

The radioisotope teletherapy units have the advantage over other high energy therapy machines of being economical to install and simple from the engineering standpoint. This advantage led to the rapid increase in their use in many countries and opened up possibilities of applying high energy radiotherapy in less developed areas. However, this rapid development also led to new problems which would not have arisen had these new radiation sources not been accessible to inexperienced persons.

According to information at hand, teletherapy units are manufactured in twelve countries:† Canada, Czechoslovakia, France, Federal Republic of Germany, Hungary, Italy, Japan, Netherlands, Sweden, United Kingdom, USA, and USSR. There are more than 50 different designs of cobalt units and at least 16 different models of cesium units. Some of these are standard types and some are custom made.

There are now over 1,000 teletherapy units, mainly cobalt, in use in various parts of the world. These figures are still rising and, no doubt, will continue to rise as long as irradiation remains an accepted method of treatment of cancer. At present, cobalt teletherapy might be well considered as one

of the most important radioisotope applications.

SOURCE ACTIVITY REQUIRED IN TELETHERAPY UNITS

In the past there have often been discussions on the designs of collimator, shutter mechanism, etc., of teletherapy units. In reviewing the present various models of cobalt units, it has been observed that they could be classified into three main groups according to their source loading capacity: (A) units with a loading capacity over 2,000 curies, (B) units with a loading capacity of 1,000–2,000 curies and (C) units with a loading capacity less than 1,000 curies. In Table I, 54 different models of cobalt units are classified in this manner: 18 under (A), 25 under (B) and 11 under (C).

The situation for cesium units is somewhat different. The cesium units manufactured at present are mainly for sources in the range of 1,000 to 2,000 curies, which is equivalent to approximately 250–500 curies of cobalt with the same output. Seven out of 16 existing different models are custom made.

The source loading capacity is the maximum activity of radioactive material which can be loaded in the source housing of the unit and the figures in Table I are based on the information supplied by the manufacturers. However, the units of source loading capacity given by the manufacturers are in no way uniform. Some give the maximum amount of activity in curie and some others indicate the maximum output of the source in units of roentgen per hour at 1 meter (rhm) or roentgen per minute at 1 meter (rmm). Figures originally given in effective curie or rhm have been converted

* At Addenbrooke's Hospital, Cambridge, England.

† For commercially available units, see reference 3.

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TABLE I
COBALT TELETHERAPY UNITS CLASSIFIED ACCORDING TO SOURCE LOADING CAPACITY

Model and Country of Origin ¹	Loading Capacity (curie or rmm)	Source-Diaphragm Distance (cm.)	Source-Ax Distance (cm.)
A. Units with a loading capacity over 2,000 curies			
1. Eldorado Super G, Canada	200 rmm	37	—
2. Theratron F, Canada	200 rmm	37	75
3. Mobaltron I, II, III, U.K.	10,000 c	34	I 60-90 II, II 75
4. Stabilatron, U.K.	10,000 c	34	—
5. Eldorado A, Canada	160 rmm	58-80	—
6. Gilatron 6,000, Italy	100 rmm	34.5	75
7. Hunslet 5,000 Isocentric Unit, U.K.	5,000 c	...	75
8. Uranos I, Italy	5,000 c	45	80 or 85
9. Gyratron I, II, U.K.	90 rmm	35	65, 70, or
10. Theratron B, Canada	90 rmm	32	75
11. Picker C-5,000, USA	83 rmm	60	95 ²
12. Rotaray Mark II, ³ USA	66.6 rmm	30 or 28.5	60 or 75
13. Jupiter Senior, Italy	60 rmm	60	95
14. Toshiba RI-107, Japan	3,000 c	14-24	65 or 75
15. Gilatron 3,000, Italy	50 rmm	32.5	65
16. Picker C-3,000, USA	50 rmm	...	95 ²
17. Westinghouse Floor Stand ⁴ Unit, USA	50 rmm	30	—
18. Westinghouse Ring Unit, ⁵ USA	50 rmm	30	60
B. Units with a loading capacity of 1,000-2,000 curies			
1. Cobaltix, France	44 rmm	47	—
2. Hunslet Pillar Type Unit, U.K.	44 rmm	35 or 40	—
3. Hunslet Moving Field Unit, U.K.	44 rmm	35	60-80
4. Flexaray, ³ USA	41.7 rmm	31.5	—
5. Gammatron I, Germany	2,000 c	31	40-65 ⁴
6. Orbitron, U.K.	2,000 c	33	60-75
7. Shimadzu RT-2,000, Japan	2,000 c	26	58-75
8. Smit-Röntgen A, B, C, Netherlands	2,000 c	A 17-50 B 50 C 20-55	— — —
9. Uranos II, Italy	2,000 c	45	80 or 85
10. Jupiter Junior II, Italy	40 rmm	...	55
11. Rotaray Mark II, ³ USA	36.6 rmm	30 or 28.5	60 or 75
12. *Argonne Kilocurie Unit, USA	34 rmm	32.2	81.6
13. Picker V-2,000, USA	33 rmm	27	—
14. Picker C-2,000, USA	33 rmm	27	55
15. Eldorado G, Canada	30 rmm	28.5	—
16. Theratron Junior, Canada	30 rmm	26.5	55
17. Theratron C-II, Canada	30 rmm	26.5	55
18. *Ontario Johns' Rotational Unit, Canada	1,800 c	60	93
19. *Oxford Cobalt Unit (Husband & Co.), U.K.	1,500 c	35	—
20. Gammatron 2, Germany	1,300 c	28.5	55
21. *Saskatchewan Kilocurie Unit, Canada	1,100 c	...	—
22. Cobaltron (twin sources), U.K.	1,000 c and 100 c	...	—

¹ For name of manufacturer, see reference 3.² With attachment, rotating 240 degrees only.³ Unit also available with other source loading capacity.⁴ Rotating 330 degrees only.⁵ Custom made unit.

TABLE I—Continued

Model and Country of Origin ¹	Loading Capacity (curie or rmm)	Source-Diaphragm Distance (cm.)	Source-Axis Distance (cm.)
23. Hunslet Dual Purpose Unit, U.K.	22 rmm	35 or 40	—
24. Westinghouse Floor Stand Unit, ² USA	20 rmm	30	—
25. Westinghouse Ring Unit, ² USA	20 rmm	30	60
C. Units with a loading capacity under 1,000 curies			
1. Flexaray, USA	16.6 rmm	31.5	—
2. Shimadzu ST-600 M II, Japan	600 c	25	—
3. Hitachi TI-600 c, Japan	600 c	...	—
4. Toshiba RI-103 D, Japan	600 c	30 or 35	—
5. Gravicert, Hungary	500 c	20	—
6. GUT-400, USSR	250 c (400 gm. radium-equivalent)	35 and 60	—
7. Commando, USA	5 rmm	12.5	—
8. *Leiden's Unit, Netherlands	100 c	25	—
9. Bryant Symons Stationary Unit, U.K.	10-150 c	8.3-20	—
10. Deka-Curie (Telegamma-Elema), Sweden	30 c	6-10	—
11. GUT-20, USSR	13 c (20 gm. radium-equivalent)	...	—

to rmm in Table I for easier comparison.

The required amount of source activity to be loaded in a teletherapy unit depends much on the conditions under which the unit is used. The maximum amount of source activity which can be loaded in the unit depends on the shielding of the source housing, or, it may be said, on the amount of leakage radiation considered acceptable outside the housing. A high activity source is still expensive, but is generally preferred in treating deep-seated tumors, because a longer treatment distance can be used and any single treatment can be completed in a relatively short time. The advantage of using a long treatment distance in deep therapy is that favorable depth doses can be obtained. At present, a source-surface distance of 80-100 cm. is generally considered as suitable for this purpose. For the patient's comfort and efficient operation, the duration of treatment should not exceed 10 minutes. On the other hand, to avoid the hazard of high level radiation, a treatment time less than 2 minutes may be considered unsuitable.

Assuming a 200 r tumor dose is to be given to a patient in one treatment and the

depth dose at the tumor center is 60 per cent, the maximum dose at the 100 per cent point would be about 330 r. If the patient is treated at 100 cm. and the treatment time is kept within 2 to 10 minutes, the dose rate at the maximum dose point is within the range of 165 r/min. to 33 r/min. In other words, the source output should be between 165 rmm to 33 rmm. Based on this calculation, a source over 165 rmm, or 9,900 rhm, or approximately 7,400 effective curies, would not be necessary nor is it suitable for use.

About half of the 54 models of cobalt teletherapy units are built with support for moving beam therapy. Five units are built for 55 cm. source-axis distance (SAD). Four units can be used for a source-axis distance of 90 cm. or over. Moving field units with 90 cm. SAD or over, are expensive. The usefulness of units with 55 cm. SAD is limited, although they are inexpensive. Seventy-five cm. source-axis distance seems to be preferred by the majority. For delivering a dose rate of 165 r/min. at 75 cm., the source output requirement would be about 93 rmm; therefore, a 100 rmm source should be considered adequate for moving

beam units designed for 75 cm. SAD.

From the economic point of view, the heavy loss due to the decay of the source activity, when the source is not in use, is rather a waste; the higher the activity of the source loaded, the larger the waste is and consequently the more expensive the use of the unit.

Table I shows that the highest loading capacity of existing units is 200 rmm. In the last few years teletherapy units with higher and higher source loading capacity have become available. Of course, a high source loading capacity of a unit is an indication of the strength of the shielding of the source housing. As mentioned before, the loading capacity of a unit depends on the amount of leakage radiation considered acceptable outside the housing. If the value of loading capacity given for a certain source housing is lower than that of some other units, this does not necessarily mean that the shielding of the unit is inferior to others, simply because the manufacturers of other units may allow a higher value of permissible leakage radiation outside the source housing. For recommendations on the amount of acceptable leakage radiation outside the source housing of teletherapy units, see references 6, 7, and 8.

WORLD DISTRIBUTION

According to Brucer and Simon,¹ up to March 1958, the total number of teletherapy sources sold from Canada and the USA was 314. Including teletherapy units with sources supplied by other countries, such as USSR and the United Kingdom, the total number of teletherapy units in the world at that time was probably not more than 500. In 1957, Errington² estimated that 1,200 teletherapy units would be in world service by the end of 1961. Based on information available at present, the total number of teletherapy units is about 1,120. The United States, USSR and Japan are the countries which have the greatest number of teletherapy units. The total number of units in these three countries alone is about 730. According to information presently at hand, there are 75 cesium

TABLE II

ESTIMATED NUMBER OF RADIOISOTOPE TELETHERAPY UNITS IN THE WORLD IN MID-YEAR, 1961

<i>North and South America</i>	480
USA.....	386
Canada.....	36
Mexico.....	19
Argentina.....	11
Brazil.....	9
<i>Asia</i>	200
Japan.....	160
India.....	7
Philippines.....	4
<i>Europe</i>	420
USSR.....	180
Italy.....	83
United Kingdom.....	47
France.....	45
<i>Others (Africa, Oceania)</i>	20
Estimated World Total.....	1,120

teletherapy units in various parts of the world, either in use or to be installed in the near future.

Table II shows the distribution of the teletherapy units and the estimated total in each continent. The distribution of cesium teletherapy units is given in Table III.

NORTH AND SOUTH AMERICA

The number of teletherapy units in the United States has increased steadily in re-

TABLE III

NUMBER OF CESIUM 137 TELETHERAPY UNITS IN MID-YEAR, 1961

(Including units to be installed in the near future)

Argentina.....	3
Belgium.....	2
Canada.....	6
Colombia.....	1
France.....	5
Germany.....	2
Indonesia.....	1
Iran.....	1
Italy.....	11
Japan.....	2
Norway.....	1
Puerto Rico.....	1
Sweden.....	3
United Kingdom.....	13
USA.....	21
USSR.....	2
Total.....	75

cent years. A survey shows that in January, 1958, there were 169 units,⁹ in September, 1959, 280 units including 9 cesium units,¹⁰ and in June, 1961, 386 units including 21 cesium units. The latter figures were derived from the number of licenses issued. Licenses are required in the United States for the installation of teletherapy units with the exception of those owned by the U. S. Atomic Energy Commission.

The world's first two units were installed in the fall of 1951 in Canada, one at the University Hospital of Saskatchewan and the other at the London Clinic, London, Ontario. At present, there are about 30 cobalt units and 6 cesium units in Canada.

Mexico, Argentina and Brazil have 19, 11 and 9 units respectively. There are also teletherapy units in Chile, Cuba, El Salvador, Peru, Uruguay and Venezuela.

ASIA

There are at least 160 teletherapy units in Japan; some estimate the number even as high as 200. Most of the units in Japan are under 200 curies. A few units have cobalt sources over 1,000 curies, and there are only 2 cesium units. Three manufacturers produce teletherapy units in Japan; some of the Japanese units have been exported to other countries.

In other Asian countries, the most popular type is the moving beam unit with 55 cm. source-axis distance. Some of these units are gifts under the Colombo plan, or from governments. There is one unit each in Burma and Ceylon, obtained under the Colombo plan; one unit in Thailand and one in Taiwan are gifts from the US Government. The GUT-400 unit in Thailand is a gift from the USSR Government, and the cesium unit in Iran is a gift from the British Government.

Although there are several moving beam units in these countries, they are, in fact, seldom used for rotation therapy because of the dosimetric problem and the lack of trained personnel.

EUROPE

It is estimated that there are about 180 radioisotope teletherapy units in the USSR.

They consist mainly of type GUT-400, which is loaded with a cobalt source of 400 gm. radium-equivalent. Italy has the next highest number of teletherapy units in Europe, with about 75 institutes equipped with one or more high energy radiation apparatus. There are about 72 cobalt units, 11 cesium units, ten 15 mev. betatrons, two 31 mev. betatrons and one 2 mev. Van de Graaff generator. Most of the cobalt units in Italy have a source activity of 1,000–2,000 curies.

France has about 40 cobalt units and 5 cesium units and there are about 34 cobalt units and 13 cesium units in the United Kingdom. The above mentioned four countries have a total of about 360 units.

There are at least 60 more units in Germany, the Netherlands, Sweden, Switzerland and other European countries.

INTERNATIONAL COLLABORATION

In the program of the International Atomic Energy Agency (IAEA) it has been pointed out that, in view of the many uses already found in technologically advanced countries for radioisotopes and radiation sources in research and in industry, agriculture and medicine, the Agency might be able to make its greatest immediate contribution to the welfare of many of its Member States by assisting them to acquire the knowledge and skills needed to make full use of radioisotopes and radiation sources.

At the beginning of 1959, the IAEA made an inquiry on the present world-wide situation with regard to the use of high energy radiation sources for radiotherapy. Questionnaires were sent out to a number of radiotherapy centers in various countries. It was then intended to submit the results of this inquiry and certain recommendations which might arise from them to a panel for consideration.

In August, 1959 a study group was organized jointly by IAEA and the World Health Organization (WHO) and convened in Vienna under the chairmanship of Prof. Windeyer. Recommendations were drawn up by this study group with a view

to giving practical guidance on basic requirements for using radioisotope teletherapy or supervoltage radiation, especially to those countries where radiotherapy is not yet firmly established. The study group considered that its basic recommendations would be of value to: (1) all authorities who carry responsibilities for radiotherapy in the treatment of cancer; (2) those who are considering the establishment of radiotherapy centers; (3) practicing radiotherapists; and (4) practicing radiation physicists.

Subsequently, these recommendations were published together with some background information obtained from the above mentioned inquiry.⁴ These recommendations are now available in several languages, including English, French, Spanish, Russian, Chinese, German and Italian. Furthermore, these recommendations have been endorsed by the Scientific Committee on Radiology of the Ministry of Health of USSR, which has taken them into account in planning their future program.

At the same time, the Secretariat of the IAEA compiled a booklet⁵ containing specifications of teletherapy units available on the market, the supply situation of teletherapy sources and prices.

In view of the fact that at present a great number of radioisotope teletherapy units is used in places which have neither the staff nor the facilities to make their own dosimetric measurements, the IAEA has already been requested by its Member States on several occasions to provide assistance in this respect. The above mentioned study group also recommended that high priority should be given to the investigation of problems of dosimetry in clinical practice. Early in 1960, the IAEA started a survey of existing data for dose distributions with high energy radiation in radiotherapy. The survey was carried out in cooperation with several national organizations, such as the American Association of Physicists in Medicine, the Hospital

Physicists' Association in the United Kingdom, the Swedish Hospital and Health Physicists' Association, and individuals working in this field. A standard questionnaire consisting of three parts, "single field," "multiple and moving field," and "equipment in use or planned," was drawn up and sent out by these organizations and individuals to major radiotherapy centers in their respective countries.

In November, 1960 participants in this project were invited to a panel meeting on "Physical Data for Dose Distributions with High Energy Radiation" in Vienna. The main purpose of this panel was to review the data and information collected from this survey and to draw up some recommendations with special consideration to making the existing data and charts accessible for extensive use on an international basis.

This panel has recommended that the IAEA should act as an International Clearing House for providing physical data and information on radiation dose distributions. It has also recommended the preparation of several publications, such as an international catalogue of existing single field isodose charts, and atlases of representative dose distributions of single, multiple and moving fields for teaching and reference purposes. The report of this panel was also published.⁶

Another important aspect of clinical dosimetry is the international comparability of dosimetric data. Another Study Group on the Standardization of Radiological Dosimetry for Radiation Beams met in Geneva in April, 1961, jointly sponsored by IAEA, WHO and ICRU. The results of this meeting will be reported elsewhere at a later date.

The above gives a short account on some work done by the IAEA in the field of medical application of radiation sources in the last two years. It is hoped that, with the continuous cooperation of radiotherapists and physicists in all countries, this work will continue not only in the interest

of science but also for the welfare of mankind.

SUMMARY

A classification has been made of the different types of radioisotope teletherapy units used in various countries according to their loading capacity in curies. There are 18 models of cobalt units with a loading capacity of over 2,000 curies, 25 models with a capacity between 1,000–2,000 curies and 11 models with a loading capacity under 1,000 curies. The source activity required and its loading are discussed.

Since the first 2 cobalt teletherapy units were installed in Canada in 1951, the number of units in use has increased to over 1,000. There are about 75 cesium units. The countries having the greatest number of units are USA, USSR and Japan, in that order. The number of units in each continent has also been estimated.

One of the functions of the International Atomic Energy Agency is to assist research on and development of the use of radioisotopes for medical purposes. A short account is given on the activities of the IAEA in the field of radioisotope teletherapy.

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EDITORIALS

A CONCEPT OF RADIOSENSITIVITY

BIOLICAL concepts of radiosensitivity were formulated within ten years of the discovery, in 1895, of the existence of the x-rays. These concepts were immortalized in the scientific literature of 1906 by Bergonié and Tribondeau.⁸ Their work has recently been translated into English²⁰ and the basic concept of radiosensitivity of Bergonié and Tribondeau, which has been given the status of radiobiological "law," may be quoted, in the words of the translation, as:

"X-rays are more effective on cells which have a greater reproductive activity; the effectiveness is greater on those cells which have a larger dividing future ahead, on those cells the morphology and function of which are least fixed."

This concept may be freely interpreted to mean that those cells which have a greater reproductive activity than other cells have also a greater mitotic rate and that those cells which have a larger dividing future ahead, whose morphology and function are least fixed, are the "stem" cells of origin, as, for example, the germinal and basal cells of the genetic, cutaneous, and intestinal epithelia and the precursor cells of hematopoietic tissue. Five decades of clinical radiotherapy experience allowed, or so it seemed, the classification of normal and malignant human cells according to a scale of relative radiosensitivities.¹

This concept, this basic "law," of radiosensitivity ought to be re-examined in the light of the theoretic and experimental radiobiological findings available today, fifty-five years later, for the classic approach to human cancer radiotherapy has rested largely upon this conceptual basis of Bergonié and Tribondeau. The importance of a periodic re-evaluation of a given con-

cept is that applications related to the concept tend to become fixed in practice, whereas the evolution of a new concept may carry with it implications for the concurrent modification of applications. What, then, is a contemporary conceptual basis of radiosensitivity?

The biological objective of human cancer radiotherapy is the selective and permanent cessation of cell division for when this occurs individual cells neither survive nor do cell lines proliferate indefinitely. It is just this end point upon which rest contemporary quantitative radiobiological observations of the effects of irradiation upon the dynamics of populations of cells.^{9,17,23,27} It is to be expected that in those populations of cells which have a relatively high mitotic rate, those populations which "have a greater reproductive activity," the radiation injury to reproductive capacity would simply be more readily and more quickly manifest without necessarily implying greater inherent radiosensitivity. It is simply that the apparent radiosensitivity, the immediately observable phenomenon, seems greater in the high-mitotic rate populations. The effect of this time sequence of events is seen quite strikingly in human irradiation where adult nervous tissue (non-dividing) and connective tissue (slowly dividing, low-mitotic rate) are said to be radioresistant while hematopoietic tissue (rapid-turn-over) is said to be radiosensitive. The situation is found to be quite different, however, when the radiation responses of neuroblasts¹¹ or of human fibroblasts²² are studied. Further, differences in radiosensitivity are not demonstrable when the irradiation responses of a number of different mammalian cell lines maintained under similar conditions of cell reproduction have been compared.²⁵

When, for example, a rapidly growing massive lymphoma filling half of the thorax and a 2 cm. in diameter squamous cell carcinoma cervical lymph node metastasis are irradiated with equal doses of roentgen rays, the clinical effect in the former will be spectacular and prompt but in the latter only moderate and delayed. These different clinical responses can be explained simply on the bases of mitotic and cell turnover rates and the time sequence of the demonstrable effects without invoking any real difference in cell radiosensitivity. Finally, it may be surmised that the nuclear DNA is the sensitive "target" material for the pertinent radiation response, reproductive capacity, and that, whatever is the nature of the "biological clock" which controls the rate of nuclear DNA synthesis and the time sequence of cell division, it is not reflected in normally occurring compositional or structural differences in nuclear DNA so far regularly demonstrable by biochemists. One can only conclude, therefore, that there is a striking similarity of inherent radiosensitivity of mammalian cell lines of diverse origins, that this inherent radiosensitivity is a property of the nuclear DNA, and that this inherent radiosensitivity can only be modified by modification of the nuclear DNA itself.

That such modification of the nuclear DNA and, in turn, of inherent radiosensitivity may, indeed, be effected seems to be established by the radiobiological observations made in quantitative mammalian cell systems under both *in vitro*^{19,20} and *in vivo*¹⁰ conditions by the substitution, through normal enzymatic anabolic processes, of a halogenated deoxyuridine riboside in the nuclear DNA. This substitution of a relatively heavy atom results in increasing the inherent radiosensitivity, perhaps by some disturbance of physico-chemical equilibrium of the nuclear DNA for the greatest effect is associated with the halogen of highest atomic number. It is highly questionable, however, whether the chemical modification of any cellular component other

than the nuclear DNA results in actual modification of radiosensitivity. This, then, is the concept given the name of *inherent radiosensitivity*, a property residing in the nuclear DNA and subject to modification only as the nuclear DNA is itself modified.

There are several biological and irradiation conditions which affect the radiation response quantitatively without any prior alteration of the composition of the nuclear DNA. Variation of the radiation response related to these extraneous factors is given the name of *apparent radiosensitivity*. These other conditions are the dose rate, the oxygen effect, the concentration of energy transfer events and associated reactive radiochemical species, and, in respect to tumors, volume.

It has long been known that populations of cells, *e.g.*, tumors, may recover from radiation effects and a quantitative concept of the degree of this recovery has been formulated for human cancer radiotherapy.² The unit cellular basis of this recovery phenomenon has, however, only recently been established *in vitro* by showing that the repair of sublethal radiation injury is completed before the first postirradiation division.¹⁸ These general findings have been confirmed quantitatively *in vivo*.⁹ The radiobiological principle of repair of sublethal cell injury implies that injury has to be, so to speak, accumulated before the lethal effect, the permanent cessation of cell division, is manifest. In other words, this injury is not a single, all or none, event but an accumulation of events; there exists a threshold level of injury. This threshold condition obtains in respect to irradiation with x-rays and electrons for mammalian cells where the nuclear DNA has not been chemically modified. That this threshold condition may not obtain when the nuclear DNA has been modified by incorporation of a halogen is suggested by the radiobiological experiments previously referred to¹⁰ and it does not obtain when irradiation is with high specific ionization (high LET) radiations.^{3,7} Because of this threshold injury phenomenon and associated

cell recovery, the effects of divided doses of x-rays on populations of cells, whether these are free cell cultures or organized as tumors, are not fully cumulative. The effect of manipulation of the interrelationship of dose and time in human cancer radiotherapy in the hope that the partially cumulative effects of irradiation would differ sufficiently from normal tissue to tumor tissue to result in differences in apparent radiosensitivity has been extensively studied.^{4,13,15} On the basis of the evidence, one must conclude, however, that there are not important differences in radiosensitivity which become manifest by such manipulation of dose and time.⁵ On the bases of the radiobiological studies of the dynamics of cell populations previously referred to, important differences are not to be expected because the thresholds of injury of human cell culture lines show no marked differences. On the other hand, absolute changes in the apparent radiosensitivity of a particular cell line do occur if a given dose is administered over an extended period of time in fractions at intervals rather than as single exposure of short duration. Certain theoretic considerations and other implications of these radiobiological phenomena for human cancer radiotherapy have been expertly treated.^{16,24}

Radiation injury is produced along the tracks of ionizing particles and its degree is related to the spatial relationships of the energy-exchange events associated with ionization and excitation along these tracks. These energy-exchange events produce, in turn, reactive radiochemical species in concentrations which are both proportional to the spatial relationships of the energy-exchange events themselves and related to the presence or absence of oxygen, for the presence of oxygen may increase the yield of the reactive radiochemical species. The spatial relationships of the energy-exchange events are called the specific ionization (or linear energy transfer, LET) of the radiation and the relationship of oxygen to the concentration of reactive radiochemical species is called the oxygen effect. The

effect of the presence of oxygen is substantially greater in the case of low specific ionization than in the case of high specific ionization radiations. X-rays and electrons are low specific ionization radiations; most accelerated particles are high. The oxygen effect in the case of the former is great and the effect of oxygen on the apparent radiosensitivity of mammalian cell lines to x-rays, in both *in vitro*¹⁴ and *in vivo*⁹ studies, has been shown to result, in respect to anoxic irradiation, in a response ratio of almost 3:1. The implications of the oxygen effect on apparent radiosensitivity have been reviewed.²¹ Similar radiobiological studies of the effects of high specific ionization radiations on the dynamics of mammalian cell populations and their apparent radiosensitivity have been performed to only a very limited degree with *in vitro*⁷ and *in vivo*⁸ quantitative cell systems. These limited studies suggest that there are two effects of these high specific ionization radiations on apparent radiosensitivity, one being the attainment of the same apparent radiosensitivity in the absence of oxygen as is attained with x-rays in the presence of oxygen⁸ and the other being the elimination of the threshold region of the radiation response, this latter implying that injury is not repairable and, therefore, that divided doses are fully cumulative. There are, then, these two effects of high specific ionization radiations, the one being the increase of response in conformity with the response to low specific ionization radiations under conditions of oxygenation and the other being the elimination of the threshold response. These effects occur without any prior modification of inherent radiosensitivity.

Tumor volume itself has an important effect upon the apparent radiosensitivity of populations of cells. The larger the tumor the greater, in general, is the number of viable cells and, therefore, the less the probability that a given dose of radiation will destroy the total number of cells. The larger the tumor the more likely, in general, that the blood supply of portions of it will

be compromised and, therefore, that these portions will be relatively hypoxic. These two characteristics, cell number and the oxygen effect, working either singly or in combination, affect the apparent radiosensitivity of organized populations of cells. The theoretic and practical implications of the relationship of tumor size to apparent radiosensitivity have been described.^{21, 22, 29}

A distinction should be made, in reference to human cancer radiotherapy, between what is meant by modification of the radiation response and what is meant by modification of radiosensitivity, in the sense in which concepts of inherent and apparent radiosensitivity have been developed above. The modification of the over-all radiation response is dependent upon many factors.⁶ The widespread use of certain pharmacologic agents—the alkylating agents, the antimetabolites, the antibiotics, in various combinations with radiotherapy may and probably does modify the over-all patient radiation response. Certain other pharmacologic agents modify the radiation response in the direction of “protection” and it is probable that many of these latter agents produce their effects simply by reacting selectively with reactive radiochemical species or with oxygen. It has not been shown, however, that any of these agents modify inherent radiosensitivity in the sense which has been developed here. These considerations suggest, then, that a more direct attack should be made on the nuclear DNA in the sense of effecting compositional or structural changes in the DNA, such as occur with the thymidine congeners discussed above. Fast neutrons, relatively high specific ionization radiations producing most biological events by recoil protons, may be generated in a variety of energies suitable for human cancer radiotherapy. The use of fast neutrons in human cancer radiotherapy has been investigated and condemned²⁶ but this was at a time when the dosimetry and the geometric relationships of neutron absorption in tissue were uncertain and when the current radiobiological concepts of thresholds and ap-

parent radiosensitivity were unknown. These considerations provide a basis for the re-exploration of the use of fast neutron beams in human cancer radiotherapy. The oxygen effect, in respect to high oxygen pressure irradiation, on apparent radiosensitivity is being exploited in human cancer radiotherapy research studies¹² but the converse, irradiation in the hypoxic or anoxic state, is not. And it is interesting to speculate on what effects might occur if both inherent radiosensitivity and apparent radiosensitivity were modified simultaneously.

In conclusion, current radiobiological theories and findings suggest the formulation of a new concept of radiosensitivity, a dual concept of inherent and apparent radiosensitivity. Inherent radiosensitivity is a property of the nuclear DNA with little, if any, differences among different mammalian cell lines but subject to modification by modification of the nuclear DNA itself, while apparent radiosensitivity is a condition of the circumstances of the irradiation and of the parameters of the observed responses. We may redefine radiosensitivity, then, as the condition of cell radiation response obtaining as a consequence of both intrinsic characteristics and extrinsic conditions. This conceptual re-examination of radiosensitivity and the redefinition of it carry implications for both the theoretic possibility of modifying radiosensitivity and the rational and practical means for so doing.

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THE UNDERGRADUATE TEACHING OF RADIATION THERAPY

“UNDERGRADUATE teaching of neoplastic diseases, both in time and content, is not commensurate with the importance of the disease, which now ranks second as a cause of death in this country.” Although this statement was made several years ago by the National Advisory Cancer Council after evaluating fifty-five medical school programs, it still holds true today. Since better than average interns frequently lack an adequate understanding of malignant disease, this, too, would seem to indicate that the medical school curriculum does not provide adequate coverage of this subject. The Council concluded that the subject was too broad to be under the control of any single division of the medical faculty and that no one man can master the whole field of cancer or be capable, by himself, of giving comprehensive instruction in cancer prevention, diagnosis, treatment, and after care.

One of the weak links in the chain of cancer instruction in medical schools is the omission of a course in Radiation Therapy from the curriculum. The reasons for this omission are due to three common factors according to Buschke, as presented at the recent meeting of the American Club of Radiotherapists. Firstly, there is a block against the teaching of radiation therapy because of the emphasis on technical factors and association with hopeless cases. Secondly, there is a lack of teaching due to inertia of faculty members and inadequate staff to teach the subject properly. Thirdly, there may be ignorance on the part of internists and surgeons concerning the value of radiation therapy in cancer management.

To develop a good teaching program, a radiologist must be aware of the needs of the student and must have an interest and capacity to communicate his ideas to others. At the undergraduate level, the course, ideally, should be one of Oncology rather than Radiation Therapy *per se*. The

radiotherapist is eminently qualified to teach oncology in major university medical centers since, as a rule, he sees and treats more cancer patients than the surgeon or the internist. He is frequently responsible for the care of a much larger number of patients who are referred by many colleagues in different disciplines. The cases of cancer he encounters cover a broad spectrum of all types and stages of this disease. To be competent in practicing radiation therapy, he must not only be thoroughly familiar with radiotherapeutics but also with the indications for surgical, hormonal, and chemotherapeutic measures.

The following four basic principles must be used to establish a solid medical school program in Radiation Therapy:

1. The course in Oncology should be organized so that the radiotherapist is responsible for a major part of the teaching in conjunction with the surgeon, internist, and pathologist.

2. The second principle is that the teaching of Radiation Therapy should emphasize the indications and contraindications for therapy and *not* radiotherapeutic techniques. The emphasis should be on the care of the patient with cancer rather than on physics, isodose curves, and high-energy instrumentation which tends to reduce the clinical impact of the discipline.

3. The third principle, which is the key message of the radiotherapist, is that radiation therapy can cure cancer and that, in a large number of selected cases, it is the treatment of choice. This should be amplified and demonstrated in every possible way, since the present impression one gains from speaking to interns and residents from various areas of the country and in our own University Hospital is that the radiotherapist sees only hopeless patients and deals with inoperable or with residual and recurrent cancer after surgery.

4. The fourth principle is that of estab-

lishing contact between the Radiation Therapy Department and medical students so that they become actively involved in the workings of the Department and understand its operation at all levels. This can be done in a number of ways and, depending on the local situation, can be implemented at different times. One of the suggestions of Dr. Henry S. Kaplan at Stanford University is that of offering summer research fellowships for students in radiobiologic subjects.

The teaching of Oncology can be oriented in one of three ways in the medical school curriculum.

1. Horizontal teaching: Here, the instruction in cancer is carried out independently and without interdepartmental coordination by a medical school department to the extent that the disease is the concern of the department.

2. Vertical teaching: In this case the teaching of cancer is through an interdepartmental coordinated approach.

3. "En block" teaching: This means that a block of time, usually in the clinical period, is reserved for concentrated efforts of all departments concerned to both orient and instruct the student.

The National Cancer Institute study "A survey and analysis of the cancer teaching programs of thirty-one schools of Medicine in the United States," by Wilcox¹ should be of interest to all radiologists involved in teaching. The surprising finding of this study was that senior students exposed to departmental oriented curriculum scored significantly higher in testing than those in interdepartmental programs; the reverse was true in the sophomore students. This could be interpreted to mean that pre-clinical sciences lend themselves better to an interdepartmental approach, whereas in the third and fourth years the clinical program might better be done on a departmental level.

¹ Wilcox, N. Elane, Ph.D. A survey and analysis of the cancer teaching programs of thirty-one schools of Medicine in the United States. University of Southern California School of Medicine Printing Department. Investigation supported by the National Cancer Institute.

A sample curriculum for teaching undergraduates Radiation Therapy and its related subjects could include:

First year. An introduction to the use of radioisotopes. This can be integrated with the Biochemistry and Physiology courses.

Second year. A coordinated course in Radiobiology in which the interreaction of ionizing radiation and biologic systems is explored from the point of view of the different basic sciences. The physical event is translated successively into chemical and biochemical events which result in biologic injury. The hazards of radiation exposure are explained. A minimum of 10 lectures is advised to accomplish this purpose.

Third year. A strong departmental program presenting the principles of radiation therapy, stressing clinical indications and limitations and not techniques. Organization is based on different anatomic sites and organ systems and includes a minimum of 10 hours or, ideally, 20 hours.

Fourth year. An interdepartmental as well as a departmental approach is advised including Tumor Conferences, Tumor Board Meetings, and Tumor Clinics in which *current cases* are presented for discussion by all concerned. These seminars and symposia should be held at regular intervals so that the team approach to cancer is recognized by the student. Elective clerkships and visiting lecturers in radiation therapy allow for opportunities for the students to develop deeper interests by exposure to stimulating ideas.

Elective teaching programs will have a number of far-reaching effects in the field of radiation therapy. They will provide for informed practicing physicians in the future, who will be more fully aware of the potential benefits of radiation therapy. More important, a stimulating program will act as a source of future recruitment for radiotherapists without which the specialty will flounder rather than flourish.

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GIOACCHINO FAILLA

1891-1961

THIS country lost one of its most illustrious radiological physicists when Dr. Gioacchino Failla was killed in an automobile accident on December 15, 1961. Dr. Failla was not only responsible for many of the most outstanding achievements in a broad field of science; it was

largely due to his imagination and pioneering efforts that radiological physics as a discipline of great depth could contribute in many important ways to radiological medicine and radiobiology.

Gioacchino Failla was born on July 19, 1891 in Castelbuono, Palermo, Italy and

was brought to the United States in 1906. He entered Columbia University in 1911 and received his E.E. degree in 1915. He then joined the New York Memorial Hospital in 1915 and remained with this institution until 1943 when he became Professor of Radiology and Director of the Radiological Research Laboratory at Columbia University. He retired from Columbia in 1960 and became Senior Physicist Emeritus at the Radiological Physics Division of the Argonne National Laboratory. He received his A.M. degree from Columbia University in 1917 and upon recommendation of Mme. Curie his D.Sc. degree from the University of Paris in 1923.

It is extremely difficult to present a summary of Dr. Failla's professional accomplishments—not only because of their great number and variety but also because of the many inspiring ideas and useful advice he so generously gave to his collaborators and other colleagues. And while he has written numerous papers, much of his work remains unpublished.

Dr. Failla's engineering talents were most valuable in the adaptation of radiation emitting substances and devices into practical sources for therapy and radiobiology. He developed the first radon plants at Memorial Hospital and then invented the radon gold seed technique. He designed the first radium "bomb" having a shutter and the first to be shielded by mercury. He designed a number of other radium and isotope teletherapy units including a multi-source radium unit for the Roosevelt Hospital in New York and recently a highly efficient cesium irradiator for the Woods Hole Marine Biological Laboratory. He invented the 2 tube, self-rectified x-ray circuit and built a number of such installations as well as a number of high voltage x-ray units. He is also responsible for many accessory devices such as the "water tank" window, adjustable x-ray collimators, safety switches, and positioning devices. His designs were prime examples of ingenuity and effectiveness.

Gioacchino Failla made decisive contri-

butions in the establishment of the concepts of exposure dose and absorbed dose. Perhaps his most brilliant achievement in the field of experimental dosimetry was his transformation of the ionization chamber—ordinarily a simple and pedestrian device—into a bewildering multitude of shapes and types. He conceived the extrapolation chamber, the tissue equivalent ionization chamber, the wall-less ionization chamber, the liquid electrode chamber, the 2 pi vacuum chamber for the measurement of β -ray activity, and a host of lesser types too numerous to mention. He pioneered in the measurement of the minute currents produced by ionization chambers and invented such instruments as the floating grid vacuum tube electrometer, the rotating potentiometer current compensator, and the first ionization chamber with flexible leads.

It was unavoidable that Dr. Failla should become greatly interested in radiobiology. Virtually throughout his entire scientific career he had at least one radiobiologist at his laboratory and it is particularly in this area that the magnitude of his contribution is difficult to document since he made numerous important suggestions to his colleagues in most major areas of radiobiology. He did publish papers on such subjects as relative biological effectiveness, osmotic imbalance as result of irradiation, and carcinogenesis and aging.

All of this work was performed simultaneously with extensive and distinguished services to the scientific community and to the nation. Gioacchino Failla was Assistant to the Scientific Attaché at the Rome Embassy as early as 1918. He served in a multitude of capacities with virtually every important society in his field and was the moving spirit in the founding of the Radiation Research Society. He served the Manhattan District and later the Atomic Energy Commission in a great number of important projects. He was Consultant to the U. S. Public Health Service, the Veterans Administration, a number of National Laboratories and many other organizations.

Dr. Failla's activities in the field of radiation protection were of cardinal importance. He was associated from the beginning with the National Committee on Radiation Protection and its predecessor, the National Advisory Committee for X-ray and Radiation Protection. He served on the Main Commissions of both the ICRP and the ICRU. He proposed the first generally accepted "tolerance dose" of 0.1 r per day and was Chairman of the respective committees and subcommittees of the ICRP and NCRP that decided on subsequent reductions of this figure. He is principally responsible for the authorship of NCRP Handbook 59 which, although published seven years ago and mostly written well before then, contains the basic concepts and tenets of current protection philosophy and expresses them with exceptional lucidity.

The vast spectrum of achievements outlined above requires extraordinary gifts of mind and character and to anyone who knew him, Dr. Failla was a truly great man. He was therefore also a humble and a kind man. The path of his life touched that of many others. These men and women came from all stations of life, but he had gifts for all of them, whether they be in the form of wisdom, knowledge or kindness.

Gioacchino Failla and Marie F. Muller married in 1925 and had two daughters who since have married and have children of their own. The first Mrs. Failla died in

1936. Patricia McClement married the "Chief" in 1949 and their marriage was singularly happy because of the personal charm and professional competence of both partners.

The world of science has expressed its indebtedness to Dr. Failla many times. He was awarded the Leonard Prize of the American Roentgen Ray Society and the Janeway Medal of the American Radium Society, the Caldwell Medal of the American Roentgen Ray Society, the Gold Medal of the Radiological Society of North America, and the Ewing Society Medal. He received an Annual National Award from the American Cancer Society, an honorary doctorate from the University of Rochester, and he was elected an honorary member of the British Institute of Radiology. The last recognition bestowed upon him was an honorary membership in the Radiological Society of North America. After a special scientific session in celebration of his seventieth birthday and upon presentation of a scroll, Failla remarked that he anticipated serving science for years to come. In view of his undiminished vigor and youthfulness he merely expressed a universal conviction. His fatal accident only 15 days later was therefore a terrible shock to all of us. Yet our bitter sorrow over all we have lost must be tempered by our deep gratitude for all we were given.

HARALD H. ROSSI, PH.D.



NEWS ITEMS

COURSE IN CLINICAL USE OF RADIOACTIVE ISOTOPES

A course in the clinical use of radioactive isotopes will be given under the supervision of Dr. Sergei Feitelberg and Dr. Edith Quimby of the Department of Radiology, Columbia University, New York City, from June 4 through June 29, 1962. This is a full-time course which includes lectures, experimental laboratory exercises, clinical rounds and clinical measurements on patients and on specimens. In addition to Drs. Feitelberg and Quimby, the teaching staff will include a number of invited lecturers from the New York area, each presenting material in his own special field.

Enrollment in the class is limited to 20; the fee is \$300.

Inquiries should be addressed to Dr. Sergei Feitelberg, Mt. Sinai Hospital, Fifth Avenue at 100th Street, New York, New York.

COURSE IN RADIATION THERAPY IN DERMATOLOGY

A two month course in basic physics and the practical use of radiation therapy in

dermatology will be offered at the Queens Hospital Center by the Radiation Medicine and Dermatology Departments. The course will be held Wednesdays (5:30 to 7:30 P.M.) from April 4, 1962 to May 23, 1962. The tuition fee is \$75.00.

For further information, please apply to Dr. Philip J. Kahan, Supervising Medical Supt., Queens Hospital Center, 82-68 164th Street, Jamaica 32, New York.

JOSEPH AND SAMUEL FREEDMAN LECTURE

On Saturday and Sunday, April 28 and 29, 1962, Dr. John Evans, Director of the Department of Radiology, New York Hospital, Cornell Medical Center, will deliver the 12th annual Joseph and Samuel Freedman Lecture in Diagnostic Radiology at the University of Cincinnati College of Medicine. There will be no charge for the lectures.

Radiologists desiring to attend are requested to write Dr. Benjamin Felson, X-Ray Department, Cincinnati General Hospital, for further details.



NATIONAL BUREAU OF STANDARDS

SCATTERING FROM A COBALT 60 CALIBRATING SOURCE

IT IS often assumed that gamma radiation beams from large cobalt 60 sources contain 1.17- and 1.33-mev. photons only. However, energy degradation resulting from Compton scattering of the radiation produces a spectrum of many energies. In calibration work, especially in the inter-comparison of instruments in different laboratories, the ability to define the spectrum is important, as many instruments are energy dependent. It is also important to know the radiation spectrum in therapeutic treatments, as the beam energy, and thus the dose absorbed in the patient's body is dependent upon the amount of scattering.

L. Costrell of the National Bureau of Standards has made an experimental determination of the amount and energy of scattered radiation coming from large cobalt 60 sources. The results of this determination can be used to estimate the amount of scattered radiation arising in the various components of typical multicurie calibrating and radiology sources.

Scattering can arise in four components of a cobalt 60 source—the source material itself, the capsule, the head, and the collimator. To determine the amount of scatter arising in each of these components, measurements were made on a series of sources, fabricated to simulate a wide range of conditions.

Measurements of beam spectra were made with a scintillation spectrometer, the detector of which consisted of a thallium-activated sodium iodide crystal 4 in. long and 5 in. in diameter, and a 5-in. photomultiplier tube. A 12-in.-long lead collimator, placed in front of the crystal, limited the diameter of the impinging beam to 1.5 in. The spectra were accumulated in one-half the memory of a 256-channel pulse height analyzer; the background spectrum was recorded in the other half and subtracted from the data of each

run. A tiny cobalt cylinder containing about 1 mc of cobalt 60 was used to determine the response of the detector to an essentially zero-scatter source.

Procedure. A series of steps was required to determine the scattered radiation spectrum for each source. First, a curve of count-rate versus energy absorbed in the scintillator was obtained for the "zero scatter" source. Using this curve, the photofraction and detector efficiency were determined as a function of energy. Then curves of count versus energy were obtained for the various sources and normalized to the same integrated count rate in the photopeak as the zero scatter curve. The latter curve was subtracted from the normalized curve for each source and the difference curves were plotted to correspond to a total count rate of 100 in the photopeaks. The photofraction and efficiency data were used along with curves of the detector response to monoenergetic photons to construct a matrix which was inverted on a computer to "unscramble" the difference curves and give curves of scattered photons versus scattered photon energy.

This procedure was necessary because of those Compton collisions within the crystal in which the scattered photon (or its descendant) escapes from the crystal. In such cases the energy absorbed in the crystal is less than the energy of the impinging quanta. Thus, some of the counts at any given energy are contributed by gamma ray photons of higher energy. The "unscrambling" has taken this into account in converting "count-rate" curves to "incident photon" curves. Finally, curves of radiation intensity versus photon energy were obtained by weighting the number of photons in the curves by the energy and normalizing to a total intensity of 100 in the photopeaks.

Results. The results of this investiga-

tion¹ show that the encapsulated source material contributes heavily to the scattered radiation. Therefore, low-scatter multicurie sources must utilize material of high specific activity. One of the sources used, simulating a widely used teletherapy

source and consisting of a basic encapsulated source surrounded by steel shot to simulate cobalt 60 pellets, was found to scatter 13.3 per cent of the total radiation. With a head emplaced, 15.4 per cent was scattered, and with a head and collimator 14.6 per cent. The other sources, having smaller masses, scattered correspondingly less radiation.

¹ For further information, see "Scattered radiation from large cobalt 60 calibrating sources," by L. Costrell, *Health Physics* (to be published).



BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

THE PHYSICS OF RADIOLOGY. Second edition. By Harold Elford* Johns, M.A., Ph.D., F.R.S.C., LL.D., Professor of Physics and Professor of Medical Biophysics, University of Toronto; Head, Physics Division, Ontario Cancer Institute, Toronto, Canada. Cloth. Pp. 767, with many illustrations and tables. Price, \$23.00. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1961.

This book is classed as a second edition of an earlier work (1953) entitled "The Physics of Radiation Therapy" by Professor H. E. Johns which has had wide acceptance among both teachers and students of radiological physics. The earlier edition was particularly useful for its clarity of presentation of concepts, sometimes difficult for the radiologist to grasp, and its valuable guidance in practical radiological physics problems.

The present work is much more than a revised second edition; not only have many new chapters been added which justify the broader title but the previous book has been completely re-written and almost all the chapters contain considerable new material presented in a rather more sophisticated manner than before. The enlargement of the material has resulted in a volume more than twice the size of the former edition.

The new chapters include such titles as: Absorbed Dose; High Energy and Teletherapy Machines; Rotation Therapy; Clinical Use of Radioisotopes; Physical Principles of Diagnostic Radiology; Radiation Protection; Radiobiology. Each of these has been treated with the thoroughness and clarity characteristic of the earlier edition. The author's emphasis on the use of high energy and teletherapy machines for beam radiation therapy demonstrates clearly the change that has come over the "hardware" of radiation therapy in less than a decade. Dr. Johns' experience and the practical guidance offered to the reader of this volume will be of particular usefulness to the radiologist just beginning to work with high energy or teletherapy devices.

The physicists will be pleased to note the

emphasis placed on absorbed dose throughout and the many instances where examples are provided to guide the reader on the conversion from measured exposure dose in roentgens to tissue absorbed dose in rads. This is a step that must be taken with care and all the relevant data are contained in this volume to make the conversion under a variety of circumstances.

An outstanding feature of this volume is the great wealth of tables, illustrations, examples and problems provided. Most of the chapters also have very useful summaries. Two large appendices contain tables of absorption coefficients, stopping powers, conversion factors from roentgens to rads and extensive depth dose tables. The illustrations and examples will be particularly appreciated by the less well-informed reader, while much of the tabular data will be useful not only to radiologists but to many radiological physicists also.

At a time when the field of radiological physics is being subdivided more and more into subspecialties, as many other recent textbooks attest, the broad scope of the material so well presented in this volume is particularly welcome. I venture to predict that no one interested in or concerned with the field of radiological physics, whether as an active worker, student or teacher, will want to be without this volume.

W. K. SINCLAIR, PH.D.

THE BASIC PHYSICS OF RADIATION THERAPY. By Joseph Selman, M.D., Clinical Assistant Professor of Radiology, The Southwestern Medical School, University of Texas; Director, School of X-Ray Technicians, Tyler Junior College; Chief of Radiology Service, Medical Center Hospital; Attending Radiologist, Mother Frances Hospital; Consultant in Radiology, East Texas Tuberculosis Hospital, Tyler, Texas. Cloth. Price, \$14.50. Pp. 671. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1960.

This volume, like the author's "Fundamentals of X-Ray and Radium Physics" starts with a brief review of simple mathematics. A sketchy review of basic physics follows, scarcely ade-

quate for understanding applications to the field of radiology, if the book is to stand alone. The content includes interaction of radiation and matter, production and measurement of x-rays, and radioactivity. Treatment planning and dosimetry with teletherapy sources and interstitial radium or radon are also included.

Where the emphasis in the earlier book was on diagnostic radiology, here the emphasis is on therapy, except for a section on the diagnostic use of radioisotopes and one on radiobiology. Where the first book was confined strictly to physics, the present one includes some discussion of medical aspects of the radioisotope tests and of principles of radiation therapy.

Apparently in an effort to simplify the subject, the author omits some important points; some of the data are not the latest and most reliable available; and some errors have crept in. The preface states that the book is intended for second year student technicians, radiology residents, and radiologists desiring a refresher course.

LUCILLE A. DU SAULT

CARCINOMA IN SITU OF THE UTERINE CERVIX; A STUDY OF 235 CASES FROM THE FREE HOSPITAL FOR WOMEN. By Gilbert H. Friedell, M.D., Associate Pathologist, Massachusetts Memorial Hospitals; Assistant in Pathology, Harvard Medical School; Associate in Pathology, Boston University School of Medicine, Boston, Massachusetts; Arthur T. Hertig, M.D., Shattuck Professor of Pathologic Anatomy and Head of the Department of Pathology, Harvard Medical School; Consultant in Pathology, Free Hospital for Women and Boston Lying-In Hospital, Boston, Massachusetts; and Paul A. Younge, M.D., Assistant Clinical Professor of Gynecology, Harvard Medical School; Associate Chief Surgeon, Free Hospital for Women, Boston, Massachusetts. Cloth. Price, \$7.50. Pp. 154, with 98 illustrations. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1960.

With the increasing availability of routine cytologic techniques, there has been an increasing interest in the diagnosis and treatment of pre-invasive carcinoma of the cervix. This monograph reports a study of 235 cases from the Free Hospital for Women, with a comprehensive account of the historic background,

pathologic anatomy, clinical findings, cytology, and various forms of therapy employed. The excellent photomicrographs serve well to illustrate the text in a quite complete discussion of the various stages of cervical dysplasia and anaplasia.

The therapy employed included almost all conceivable types of surgery and irradiation available, both separately and in combination.

Discussion of the results is divided into three categories based on the original diagnosis which was later confirmed or changed to carcinoma *in situ*. Category I includes 86 cases which were treated originally because of a diagnosis of some nonmalignant disease. Category II (97 cases) comprises those in which the first and final diagnosis was carcinoma *in situ*. Both of these groups were treated primarily by surgery. The 49 cases in Category III were originally diagnosed as invasive squamous carcinoma and later "downgraded" to *in situ* lesions. The treatment in this group was primarily some form of irradiation.

The philosophy of treatment in the various age groups is also considered.

For physicians involved in the diagnosis and treatment of carcinoma of the cervix, this is a most worthwhile addition to their library.

DARRELL E. STATZER, M.D.

DISEASES OF THE INTERVERTEBRAL DISC AND ITS SURROUNDING TISSUES. By Reuben Rabinovitch, B.A., M.Sc., M.D., Assistant Professor in Neurology and Neurosurgery, McGill University, Faculty of Medicine, Montreal; and Assistant Neurologist, The Department of Neurology and Neurosurgery, The Royal Victoria Hospital and The Montreal Neurological Institute. Cloth. Price, \$8.50. Pp. 152, with 78 illustrations. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1961.

The author presents some original basic work on intervertebral disc disease with several cases to emphasize his ideas and a brief review of the literature. He is particularly interested in the etiology of multiple disc disease. Studies are presented on hydration and dehydration of discs and he postulates that certain general diseases, hormones or chemical changes in the body may alter the water content of the disc and thereby initiate degeneration of many discs.

A methyl green-acid fuchsin stain has been developed in order to be able to follow changes

from the healthy to the diseased disc. He believes that although trauma may sometimes be the sole etiology of ruptured disc, frequently pre-existing disease allows only minor injury or absence of trauma to cause a rupture of the disc.

Many kinds of surgical trauma have been produced to normal discs of monkeys and rabbits in order to follow the disc degeneration and repair. These have been described in detail from the roentgen, clinical and autopsy studies. A logical explanation for the predominance of symptomatic disc protrusions in the lower cervical and lower lumbar regions is given.

The book offers another stepping stone toward a better understanding of disc disease.

FRANK M. WINDROW, M.D.

BOOKS RECEIVED

ROENTGENOLOGY OF THE ABDOMEN. By Juan M. Taveras, M.D., Professor of Radiology, College of Physicians and Surgeons, Columbia University; Associate Attending Radiologist, Presbyterian Hospital, New York; and Ross Golden, M.D., Visiting Professor of Radiology, University of California at Los Angeles; Emeritus Professor of Radiology, College of Physicians and Surgeons, Columbia University. Cloth. Price, \$9.00. Pp. 184, with 151 illustrations. Williams & Wilkins Company, 428 East Preston Street, Baltimore 2, Md., 1961.

NEOPLASTIC DISEASE AT VARIOUS SITES, VOL. IV. TUMOURS OF THE OESOPHAGUS. General Editor: D. W. Smithers, M.D., F.R.C.P., F.F.R., Professor of Radiotherapy in the University of London; Director, Radiotherapy Department, Royal Marsden Hospital, and Institute of Cancer Research, Royal Cancer Hospital; Radiotherapist, Brompton Hospital, London. Cloth. Price, \$13.00. Pp. 352, with 165 illustrations. E. & S. Livingstone, Ltd., 16 and 17 Teviot Place, Edinburgh 1, Scotland, 1961.

THE ROENTGENOLOGICAL ASPECT OF NONPENETRATING CHEST INJURIES. By John Riley Williams, M.D., Fellow in Radiology, The University of Texas Southwestern Medical School, Parkland Memorial Hospital, Dallas, Texas; Formerly, Chief, Department of Radiology, U. S. Naval Hospital, Jacksonville, Florida; and Frederick J. Bonte, M.D., F.A.C.R., Professor and Chairman, Department of Radiology, The University of Texas Southwestern Medical School; Director, Department of Radiology, Parkland Memorial Hospital, Dallas, Texas. Cloth. Price, \$7.50. Pp. 135, with 31 figures. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill., 1961.

BASIC PRINCIPLES OF THE TRACER METHOD; INTRODUCTION TO MATHEMATICAL TRACER KINETICS. By C. W. Sheppard, Ph.D., Professor of Physiology, University of Tennessee Medical Units, Memphis, Tennessee. Cloth. Price, \$8.00. Pp. 282, with many illustrations and tables. John Wiley & Sons, Inc., 440 Park Avenue South, New York 16, N. Y., 1962.

THE SPINE; A RADIOLOGICAL TEXT AND ATLAS. Second edition. By Bernard S. Epstein, M.D., Chief, Department of Radiology, The Long Island Jewish Hospital, New Hyde Park, New York; Clinical Professor of Radiology, The Albert Einstein College of Medicine, New York. Cloth. Price, \$16.50. Pp. 516, with 393 illustrations. Lea & Febiger, 600 S. Washington Square, Philadelphia 6, Pa., 1962.

TREATMENT OF CANCER AND ALLIED DISEASES. VOL. V. TUMORS OF THE GASTROINTESTINAL TRACT, PANCREAS, BILIARY SYSTEM, AND LIVER. Second edition. Edited by George T. Pack, M.D., F.A.C.S., and Irving M. Ariel, M.D., F.A.C.S. Cloth. Price, \$33.00. Pp. 828, with 670 illustrations. Paul B. Hoeber, Inc., 49 East 33rd Street, New York 16, N. Y., 1962.

DIE SUPERVOLTHERAPIE; GRUNDLAGEN, METHODEN UND ERGEBNISSE DER THERAPIE MIT ENERGIEREICHEN TEILCHEN UND ULTRAHARTEN STRAHLEN. By Prof. Dr. J. Becker, Direktor des Czerny-Krankenhauses für Strahlenbehandlung der Universität Heidelberg; and Prof. Dr. G. Schubert, Direktor der Universitäts-Frauenklinik und Poliklinik Hamburg-Eppendorf. Cloth. Price, \$36.25. Pp. 584, with 421 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart, Germany, 1961. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y.

DIE AORTOGRAPHIE DES ABDOMENS AUS KLINISCHER SICHT. By Dr. med. Dieter Tillie, Facharzt für Innere Krankheiten, Röntgenologie und Strahlenheilkunde, Oberarzt an der II. Med. Klinik des Städt. Krankenhauses Berlin-Buch, Germany. Cloth. Pp. 199, with 165 illustrations. Georg Thieme Verlag, Herdweg 63, Stuttgart, Germany, 1961. In the U.S.A. and Canada, Intercontinental Medical Book Corporation, New York 16, N. Y.

ANNUAL REVIEW OF NUCLEAR SCIENCE. VOL. 11. Emilio Segrè, Editor, University of California; Gerhart Friedlander, Associate Editor, Brookhaven National Laboratory; and Walter E. Meyerhof, Associate Editor, Stanford University. Cloth. Price, \$7.00. Pp. 513, with figures and tables. Annual Reviews, Inc., Palo Alto, California, 1961.

BROOKHAVEN SYMPOSIA IN BIOLOGY. NO. 14. FUNDAMENTAL ASPECTS OF RADIOSENSITIVITY. Paper. Price, \$3.00. Pp. 308, with many figures and tables. Available from the Office of Technical Services, Department of Commerce, Washington 25, D. C., 1961.

SOCIETY PROCEEDINGS

MEETINGS OF RADIOLOGICAL SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY

Secretary, Dr. C. Allen Good, Mayo Clinic, Rochester, Minn. Annual meeting: Shoreham Hotel, Washington, D. C., Oct. 2-5, 1962.

AMERICAN RADIUM SOCIETY

Secretary, Dr. Charles G. Stetson, 350 Engle Street, Englewood, N. J. Annual meeting: Waldorf-Astoria Hotel, New York, N. Y., April 2-4, 1962.

RADIOLOGICAL SOCIETY OF NORTH AMERICA

Secretary, Maurice Doyle Frazer, 1744 South Fifty-eighth St., Lincoln, Neb.

Treasurer, Dwight Vincent Needham, 713 E. Genessee St., Syracuse, N. Y. Annual meeting: Palmer House, Chicago, Nov. 25-30, 1962.

AMERICAN COLLEGE OF RADIOLOGY

Executive Director, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Illinois. Annual meeting: Roosevelt Hotel, New York, N. Y., Feb. 7-10, 1962.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION

Secretary, Dr. Clyde A. Stevenson, Sacred Heart Hospital, West 101 Eighth Ave., Spokane 4, Wash. Annual meeting: Chicago, Ill., June 24-28, 1962.

AMERICAN BOARD OF RADIOLOGY

Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn. The Spring 1962 examination will be held at the Terrace Hilton Hotel, Cincinnati, Ohio, June 18-22, 1962 inclusive. The deadline for filing applications was January 1, 1962. A special examination in Nuclear Medicine for Diplomates in Radiology or Therapeutic Radiology and an examination in Radiological Physics will be held if there are sufficient applications. The Fall 1962 examination will be held at the Pioneer Hotel, Tucson, Arizona, the first week in December; the deadline for filing applications is July 1, 1962. Please note that at this session Nuclear Medicine will become a mandatory part of the examination. All candidates, excluding re-examinees, who are applying for examination in Radiology or Therapeutic Radiology for the December, 1962 session or thereafter must submit a Nuclear Medicine application in addition to their basic application. This applies even to those applicants whose basic applications are on file but who will not yet have appeared for examination.

AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE

Secretary-Treasurer, Charles S. Simons, University of Michigan Hospital, Ann Arbor, Mich. Annual meeting to be announced.

TENTH INTERNATIONAL CONGRESS OF RADIOLOGY

Secretary-General, Dr. Carleton B. Peirce, Royal Victoria Hospital, Montreal 2, Quebec, Canada. Meets in Montreal, Aug. 26-Sept. 1, 1962.

EIGHTH INTER-AMERICAN CONGRESS OF RADIOLOGY

Counselor for the United States, Dr. J. A. del Regato, Penrose Cancer Hospital, 2200 North Cascade Avenue, Colorado Springs, Colorado. Meeting to be announced.

ALABAMA RADIOLOGICAL SOCIETY

Secretary, Dr. Walter Brower, Birmingham, Ala. Meets time and place Alabama State Medical Association.

AMERICAN NUCLEAR SOCIETY

Executive-Secretary, Octave J. Du Temple, 86 E. Randolph St., Chicago, Ill.

ARIZONA RADIOLOGICAL SOCIETY

Secretary, Dr. Don E. Matthieson, 926 East McDowell Rd., Phoenix, Ariz. Two regular meetings a year. Annual

meeting at time and place of State Medical Association and interim meeting six months later.

ARKANSAS RADIOLOGICAL SOCIETY

Secretary, Dr. Charles W. Anderson, 1108½ Poplar, Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

ASSOCIATION OF UNIVERSITY RADIOLOGISTS

Secretary, Dr. Herbert M. Stauffer, Temple University Medical Center, Philadelphia 40, Pa. Annual Meeting: University of Indiana, Indianapolis, Ind., May 19-20, 1962.

ATLANTA RADIOLOGICAL SOCIETY

Secretary, Dr. Wilson T. Edenfield, 35 Linden Ave., N.E., Atlanta 8, Ga. Meets monthly, except during three summer months, on second Friday evening.

BLOCKLEY RADIOLOGICAL SOCIETY

Secretary, Dr. Bernard J. Ostrum, 2412 North 52nd St., Philadelphia, Pa.

BROOKLYN RADIOLOGICAL SOCIETY

Secretary, Dr. Leslie L. Alexander, 257 New York Ave., Brooklyn 16, N. Y. Meets first Thursday of each month October through May.

BUFFALO RADIOLOGICAL SOCIETY

Secretary, Dr. R. Joseph Naples, 106 Morgan Parkway, Williamsville 21, N. Y. Meets second Monday evening each month, October to May inclusive.

CENTRAL NEW YORK RADIOLOGICAL SOCIETY

Secretary, Dr. Joseph A. Head, 150 Marshall St., Syracuse, N. Y. Meets first Monday each month October through May.

CENTRAL OHIO RADIOLOGICAL SOCIETY

Secretary, Dr. Robert L. Freidman, Grant Hospital, Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

CENTRAL SOCIETY OF NUCLEAR MEDICINE

Secretary, Dr. Robert S. Landauer, Radiation Center Building, 1903 West Harrison St., Chicago 12, Ill.

CHICAGO ROENTGEN SOCIETY

Secretary, Dr. William F. Hutson, 5145 N. California Ave., Chicago, Ill. Meets second Thursday of each month, October to April except December at the Sheraton Hotel at 8:00 P.M.

CLEVELAND RADIOLOGICAL SOCIETY

Secretary, Dr. Ward D. Heinrich, Huron Road Hospital, Cleveland 12, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

COLORADO RADIOLOGICAL SOCIETY

Secretary, Dr. Seward Imes, 1845 High St., Denver, Colo. Meets third Friday of each month at Denver Athletic Club from September through May.

CONNECTICUT VALLEY RADIOLOGICAL SOCIETY

Secretary, Dr. James L. Krieger, 85 Jefferson St., Hartford, Conn. Meets first Friday in February and April.

DALLAS-FORT WORTH RADIOLOGICAL SOCIETY

Secretary, Dr. Robert D. Moreton, 816 Medical Arts Bldg., Fort Worth, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY

Secretary, Dr. Kenneth L. Krabbenhoft, Harper Hospital, Detroit 1, Mich. Meets monthly, first Thursday, October through May, at David Whitney House, 1010 Antietam, at 6:30 P.M.

* Secretaries of societies are requested to send timely information promptly to the Editor.

- EAST BAY ROENTGEN SOCIETY**
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.
- EAST TENNESSEE RADIOLOGICAL SOCIETY**
Secretary, Dr. J. Marsh Frere, Jr., 205 Medical Arts Building, Knoxville, Tenn. Meets in January and September.
- EASTERN CONFERENCE OF RADIOLOGY**
Secretary, Arrangements Committee, Dr. Bernard S. Wolf, The Mount Sinai Hospital, 11 E. 100 Street, New York 29, N. Y. Annual Meeting: Waldorf-Astoria Hotel, New York, March 29-31, 1962.
- EASTERN RADIOLOGICAL SOCIETY**
Secretary, Dr. James F. Martin, North Carolina Baptist Hospital, Winston-Salem, N. C. Meets at Mid Pines Club, Southern Pines, N. C., April 29-May 2, 1962.
- FLORIDA RADIOLOGICAL SOCIETY**
Secretary, Dr. Richard D. Shapiro, 1680 Meridian Ave., Miami Beach, Fla. Meets twice annually, in the spring with the annual State Society Meeting, and in the fall.
- FLORIDA WEST COAST RADIOLOGICAL SOCIETY**
Secretary-Treasurer, Dr. Joseph C. Rush, 1800 Druid Rd., Clearwater, Fla.
- GEORGIA RADIOLOGICAL SOCIETY**
Secretary, Dr. George W. Brown, Griffin, Ga. Meets in spring and fall with Annual State Society Meeting.
- GREATER MIAMI RADIOLOGICAL SOCIETY**
Secretary, Dr. Carl E. Balli, 907-8 Huntington Medical Building, Miami 32, Fla. Meets monthly, third Wednesday, at 8:00 P.M. at Jackson Memorial Hospital, Miami, Fla.
- GREATER ST. LOUIS SOCIETY OF RADIOLOGISTS**
Secretary, Dr. William E. Powers, St. Louis, Mo.
- HOUSTON RADIOLOGICAL SOCIETY**
Secretary, Dr. John Douglas Reeve, Texas Medical Center Library, Jesse H. Jones Library Bldg., Houston 25, Texas. Meets last Monday each month, Seminar Room, Doctors' Club of Houston.
- IDaho STATE RADIOLOGICAL SOCIETY**
Secretary, Dr. George H. Harris, Bannock Memorial Hospital, Pocatello, Idaho. Meets in the spring and fall.
- ILLINOIS RADIOLOGICAL SOCIETY**
Secretary, Dr. George A. Miller, Carle Hospital Clinic, Urbana, Ill. Meets in the spring and fall.
- INDIANA ROENTGEN SOCIETY, INC.**
Secretary, Dr. David E. Wheeler, 1500 North Ritter, Indianapolis, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.
- IOWA RADIOLOGICAL SOCIETY**
Secretary, Dr. L. L. Maher, 1419 Woodland Ave., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.
- KANSAS RADIOLOGICAL SOCIETY**
Secretary, Dr. Roger K. Wallace, Riley County Hospital, Manhattan, Kansas. Meets in spring with State Medical Society, and in winter on call.
- KENTUCKY RADIOLOGICAL SOCIETY**
Secretary, Dr. Lawrence A. Davis, 226 East Chestnut St., Louisville, Ky. Meets monthly on second Friday at Sheraton Hotel, Louisville.
- KINGS COUNTY RADIOLOGICAL SOCIETY**
Secretary, Dr. Abraham Berens, 1917 Bedford Ave., Brooklyn 25, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.
- LOS ANGELES RADIOLOGICAL SOCIETY**
Secretary, Dr. Saul Heiser, Los Angeles, Calif. Meets second Wednesday of month in September, November, January, March and June at Los Angeles County Medical Association Building, Los Angeles.
- MAINE RADIOLOGICAL SOCIETY**
Secretary, Dr. Albert A. Poulin, Thayer Hospital, Waterville, Maine. Meets in June, September, December and April.
- MARYLAND RADIOLOGICAL SOCIETY**
Secretary, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore 17, Md.
- MEMPHIS ROENTGEN SOCIETY**
Secretary, Dr. Irving K. Ettman, Kennedy V.A. Hospital, Department of Radiology, Memphis 15, Tenn. Meets first Monday of each month at John Gaston Hospital.
- MIAMI VALLEY RADIOLOGICAL SOCIETY**
Secretary, Dr. William D. Roberts, 2197 Los Arrow Dr., Dayton 9, Ohio. Meets second Friday of fall and winter months.
- MID-HUDSON RADIOLOGICAL SOCIETY**
Secretary, Dr. Joseph Sorrentino, St. Francis Hospital, Poughkeepsie, N. Y. Meets 8:30 P.M., fourth Wednesday each month, September to May.
- MILWAUKEE ROENTGEN RAY SOCIETY**
Secretary, Dr. Abraham Marck, Mayfair Professional Bldg., Milwaukee 13, Wis. Meets monthly on fourth Monday, October through May, at University Club.
- MINNESOTA RADIOLOGICAL SOCIETY**
Secretary, Dr. Donald H. Peterson, 853 Medical Arts Bldg., Minneapolis 2, Minn. Meets three times annually, in fall, winter and spring.
- MISSISSIPPI RADIOLOGICAL SOCIETY**
Secretary, Dr. Jack K. Goodrich, University Medical Center, Jackson, Miss. Meets third Thursday of each month at the Heidelberg Hotel, Jackson, at 6:00 P.M.
- MONTANA RADIOLOGICAL SOCIETY**
Secretary, Dr. John M. Fritts, Missoula, Montana. Meets at least once a year.
- NASSAU RADIOLOGICAL SOCIETY**
Secretary, Dr. Robert Tugendhaft, 100 Nowbridge Rd., Hicksville, N. Y. Meets second Tuesday of the month in February, April, June, October and December.
- NEBRASKA STATE RADIOLOGICAL SOCIETY**
Secretary, Dr. Richard Bunting, The Radiologic Center, Nebraska Methodist Hospital, Omaha 31, Nebraska. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.
- NEVADA RADIOLOGICAL SOCIETY**
Secretary, Dr. George F. Fraser, Las Vegas, Nev.
- NEW ENGLAND ROENTGEN RAY SOCIETY**
Secretary, Dr. Robert E. Wise, 605 Commonwealth Ave., Boston 15, Mass. Meets third Friday of each month, October through April at The Longwood Towers, Brookline, Mass.
- NEW HAMPSHIRE ROENTGEN RAY SOCIETY**
Secretary, Dr. Paul Y. Hasserjian, 1470 Elm St., Manchester, N. H. Meets four to six times yearly.
- NEW YORK ROENTGEN SOCIETY**
Secretary, Dr. Bernard S. Wolf, Mt. Sinai Hospital, New York, N. Y. Meets monthly on third Monday at the New York Academy of Medicine at 4:30 P.M.
- NORTH CAROLINA RADIOLOGICAL SOCIETY**
Secretary, Dr. A. B. Croom, 624 Quaker Lane, High Point, N. C. Meets in the spring and fall each year.
- NORTH DAKOTA RADIOLOGICAL SOCIETY**
Secretary, Dr. John Jestadt, Depuy-Sorkness Clinic, Jamestown, North Dakota. Meets at time of State Medical Association meeting. Other meetings arranged on call of the President.
- NORTH FLORIDA RADIOLOGICAL SOCIETY**
Secretary, Dr. Charles H. Newell, 800 Miami Road, Jacksonville 7, Fla. Meets quarterly in March, June, September and December.
- NORTHEASTERN NEW YORK RADIOLOGICAL SOCIETY**
Secretary, Dr. Lester I. Citrin, St. Mary's Hospital, Troy, N. Y. Meets in Albany area on second Wednesday of October, November, March and April.
- NORTHERN CALIFORNIA RADIOLOGICAL SOCIETY**
Secretary, Dr. Rob H. Kirkpatrick, 1219 28th St., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

NORTHWESTERN OHIO RADIOLOGICAL SOCIETY

Secretary, Dr. George Asahina, 421 Michigan St., Toledo, Ohio.

OHIO STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Chapin Hawley, 927 Carew Tower, Cincinnati, Ohio. Annual meeting May 25-27, 1962 in Akron.

OKLAHOMA STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Simon Pollack, Utica Square Medical Center, Tulsa, Okla. Meets in January, May and October.

OREGON RADIOLOGICAL SOCIETY

Secretary, Dr. George R. Satterwhite, Willamette Falls Community Hospital, 15th and Division, Oregon City, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

ORLEANS PARISH RADIOLOGICAL SOCIETY

Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY

Secretary, Dr. John N. Burkey, 555 Dental Bldg., Seattle, Wash. Annual meeting: Seattle, Washington.

PACIFIC ROENTGEN SOCIETY

Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco 8, Calif. Meets annually during meeting of California Medical Association.

PENNSYLVANIA RADIOLOGICAL SOCIETY

Secretary, Dr. Frederick R. Gilmore, Clearfield Hospital, Clearfield, Pa. Annual meeting: Pocono Manor Inn, May 25-26, 1962.

PHILADELPHIA ROENTGEN RAY SOCIETY

Secretary, Dr. Robert B. Funch, Department of Radiology, Germantown Hospital, Philadelphia 44, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

PITTSBURGH ROENTGEN SOCIETY

Secretary, Dr. Ross H. Smith, St. Margaret Memorial Hospital, Forty-Sixth St., Pittsburgh 1, Pa. Meets second Wednesday of month, October through June at Park Schenely Restaurant.

RADIOLOGICAL SECTION, BALTIMORE MEDICAL SOCIETY

Secretary, Dr. James K. V. Willson, 1100 N. Charles St., Baltimore 1, Md. Meets third Tuesday each month, September to May, inclusive.

RADIOLOGICAL SOCIETY OF GREATER CINCINNATI

Secretary, Dr. William C. Duffey, Cincinnati, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

RADIOLOGICAL SOCIETY OF HAWAII

Secretary, Dr. G. J. Liese, Queen's Hospital, Honolulu, Hawaii. Meets third Monday of each month at 7:30 P.M.

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY

Secretary, Dr. J. Stewart Whitmore, 1010 Rialto Bldg., Kansas City, Mo. Meets last Friday of each month.

RADIOLOGICAL SOCIETY OF KANSAS CITY

Secretary, Dr. Arthur B. Smith, 800 Argle Bldg., Kansas City, Mo. Meets third Thursday of each month.

RADIOLOGICAL SOCIETY OF LOUISIANA

Secretary, Dr. Robyn Hardy, 4324 Magnolia St., New Orleans 15, La. Meets annually during Louisiana State Medical Society meeting.

RADIOLOGICAL SOCIETY OF NEW JERSEY

Secretary, Dr. George H. Burke, 601 Grand Ave., Asbury Park, N. J. Meets at Atlantic City at time of State Medical Society meeting and in November in Newark, N. J.

RADIOLOGICAL SOCIETY OF THE STATE OF NEW YORK

Secretary-Treasurer, Dr. John W. Colgan, 273 Hollywood Ave., Rochester 18, N. Y. Annual meeting Apr. 4-8, 1962.

RADIOLOGICAL SOCIETY OF SOUTH DAKOTA

Secretary-Treasurer, Dr. Donald J. Peik, 303 S. Minnesota Ave., Sioux Falls, S. D.

RADIOLOGICAL SOCIETY OF SOUTHERN CALIFORNIA

Secretary, Dr. Robert Scanlan, St. Vincent's Hospital, Los Angeles, Calif.

REDWOOD EMPIRE RADIOLOGICAL SOCIETY

Secretary, Dr. Lee E. Titus, 164 W. Napa St., Sonoma, Calif. Meets second Monday every other month.

RICHMOND COUNTY RADIOLOGICAL SOCIETY

Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y.

Secretary, Dr. Robert H. Greenlaw, 260 Crittenden Blvd., Rochester 20, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY

Secretary, Dr. John H. Freed, 4200 East Ninth Ave., Denver 20, Colo. Annual meeting: Denver Hilton Hotel, Denver, Colo., Aug. 16-18, 1962.

SAN ANTONIO-MILITARY RADIOLOGICAL SOCIETY

Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets third Wednesday each month in Fort Sam Houston Officer's Club at 6:30 P.M.

SAN DIEGO RADIOLOGICAL SOCIETY

Secretary, Dr. Charles B. Campbell, 7849 A Ave., La Jolla, Calif. Meets first Wednesday of each month at the University Club.

SAN FRANCISCO RADIOLOGICAL SOCIETY

Secretary, Dr. Walter Coulson, San Francisco General Hospital, San Francisco 8, Calif. Meets quarterly at the San Francisco Medical Society, 250 Masonic Ave., San Francisco 18, Calif.

SECTION ON RADIOLOGY, CALIFORNIA MEDICAL ASSOCIATION

Secretary, Dr. William H. Graham, 630 East Santa Clara St., San Jose, Calif.

SECTION ON RADIOLOGY, CONNECTICUT STATE MEDICAL SOCIETY

Secretary, Dr. Wayne P. Whitcomb, Hospital of St. Raphael, New Haven, Conn. Meetings are held bi-monthly.

SECTION ON RADIOLOGY, MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA

Secretary, Dr. William E. Sheely, 1746 K St., N.W., Washington 6, D. C. Meets at Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

SECTION ON RADIOLOGY, ILLINOIS STATE MEDICAL SOCIETY

Secretary, Dr. William Meszaros, 1825 W. Harrison St., Chicago, Ill.

SECTION ON RADIOLOGY, SOUTHERN MEDICAL ASSOCIATION

Secretary, Dr. Seymour Ochsner, Ochsner Clinic, 3503 Prytania St., New Orleans 15, La. Annual meeting to be announced.

SHREVEPORT RADIOLOGICAL CLUB

Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

SOCIETY FOR PEDIATRIC RADIOLOGY

Secretary, Dr. Richard G. Lester, 412 Union St., S.E., Minneapolis 14, Minn. Annual meeting: Shoreham Hotel, Washington, D. C., Sept. 30-Oct. 1, 1962.

SOCIETY OF NUCLEAR MEDICINE

Secretary, Dr. Robert W. Lackey, 452 Metropolitan Bldg., Denver 2, Colo. *Administrator*, Samuel N. Turiel, 430 N. Michigan Ave., Chicago 11, Ill. Annual meeting: Baker Hotel, Dallas, Texas, June 27-30, 1962.

SOUTH BAY RADIOLOGICAL SOCIETY

Secretary, Dr. Stanford B. Rossiter, 1111 University Dr., Menlo Park, Calif. Meets second Wednesday of each month.

SOUTH CAROLINA RADIOLOGICAL SOCIETY

Secretary, Dr. George W. Brunson, 1406 Gregg St., Columbia, S. C. Annual meeting (primarily business) in conjunction with the South Carolina Medical Association meeting in May. Annual fall scientific meeting at time and place designated by the president.

SOUTHERN RADIOLOGICAL CONFERENCE

Secretary, Dr. Marshall Eskridge, Mobile Infirmary, P.O. Box 4097, Mobile, Ala.

SOUTHWESTERN RADIOLOGICAL SOCIETY

Secretary, John M. McGuire, 904 Chelsea, El Paso, Texas. Meets last Monday of each month at 6:30 p.m. in the Paso del Norte Hotel.

TENNESSEE RADIOLOGICAL SOCIETY

Secretary, Dr. B. M. Brady, St. Joseph Hospital, Memphis, Tenn. Meets annually at the time and place of the Tennessee State Medical Association meeting.

TEXAS RADIOLOGICAL SOCIETY

Secretary, Dr. R. P. O'Bannon, 402 Professional Bldg., 1216 Pennsylvania Ave., Fort Worth 4, Texas. Annual meeting: to be announced.

TRI-STATE RADIOLOGICAL SOCIETY

Secretary, Dr. John H. Marchand, Jr., Welborn Clinic, 420 Cherry St., Evansville, Ind. Meets third Wednesday of Oct., Jan., March and May, 8:00 p.m., Elks Club in Evansville.

UNIVERSITY OF MICHIGAN DEPARTMENT OF ROENTGENOLOGY STAFF MEETING

Meets each Monday evening from September to June, at 7:00 p.m. at University Hospital.

UPPER PENINSULA RADIOLOGICAL SOCIETY

Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

UTAH STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Richard Y. Card, St. Mark's Hospital, Salt Lake City, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

VERMONT RADIOLOGICAL SOCIETY

Secretary, Dr. John R. Williams, Rutland, Vt.

VIRGINIA RADIOLOGICAL SOCIETY

Secretary, Dr. Powell G. Dillard, Jr., 715 Church Street, Lynchburg, Va. Meets annually in October.

WASHINGTON STATE RADIOLOGICAL SOCIETY

Secretary, Dr. Joseph T. Houk, 14303 Ambaum Blvd., Seattle 66, Wash. Meets third Monday of each month from September through April at the University of Washington Medical School.

WEST VIRGINIA RADIOLOGICAL SOCIETY

Secretary, Dr. Karl J. Myers, The Myers Clinic-Broadus Hospital, Philippi, W. Va. Meets concurrently with Annual Meeting of West Virginia State Medical Society; other meetings arranged by program committee.

WESTCHESTER RADIOLOGICAL SOCIETY

Secretary, Dr. Anthony A. Magliene, Westchester Academy of Medicine, Section on Radiology, Purchase, N. Y. Meets on third Tuesday of January and October and on two other dates.

WISCONSIN RADIOLOGICAL SOCIETY

Secretary, Dr. Howard G. Bayley, 116 Iroquois Parkway, Beaver Dam, Wis. Annual meeting each spring in various places.

CUBA, MEXICO, PUERTO RICO AND CENTRAL AMERICA

ASOCIACIÓN DE RADIOLOGOS DE CENTRO AMERICA Y PANAMÁ. Comprising: Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica and Panamá.

Secretary-General, Dr. Julio Toriello, 11 Calle 2-37, Zona 1, Guatemala. Meets annually in a rotating manner in the six countries.

SOCIEDAD DE RADIOLOGÍA DE EL SALVADOR

Secretary, Dr. Rafael Vaga Gómez

SOCIEDAD DE RADIOLOGÍA DE GUATEMALA

Secretary, Dr. Carlos E. Escobar, 5^a Calle A 0-05, Zona 1, Guatemala.

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPIA CUBANA

Secretary, Dr. Miguel A. García Plasencia, Hospital Curie, 29 y F, Vedado, Habana, Cuba. Meets monthly at Curie Hospital.

SOCIEDAD COSTARRICENSE DE RADIOLOGIA

Secretary, Dr. James Fernández Carballo, Apartado VIII, San José, Costa Rica.

SOCIEDAD MEXICANA DE RADIOLOGÍA, A. C.

Calle del Oro No. 15, México 7, D. F.

Secretary-General, Dr. E. Alvarez Hernández. Meets first Monday of each month.

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA

Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

SOCIEDAD RADIOLOGICA PANAMEÑA

Secretary, Dr. L. Arrieta Sánchez, Apartado No. 6323, Panamá, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

SOCIEDAD RADIOLOGICA DE PUERTO RICO

Secretary, Dr. César E. Rosa-Perez, Fondo del Seguro del Estado, Parada 1, San Juan 8, Puerto Rico. Meets second Thursday of each month at 8:00 p.m. at the Puerto Rico Medical Association Bldg. in San Juan.

BRITISH COMMONWEALTH OF NATIONS

ASSOCIATION OF RADIOLOGISTS OF THE PROVINCE OF QUEBEC

Secretary, Dr. Odilon Raymond, 5400 Blvd. Gouin, Quest, Montreal, Que. Meets four times a year.

BRITISH INSTITUTE OF RADIOLOGY

Honorary Secretary, Dr. R. D. Hoare, 32 Welbeck St., London, W. 1. Meets monthly from October until May.

EDMONTON AND DISTRICT RADIOLOGICAL SOCIETY

Secretary, Dr. S. C. Windle, 105 Northgate Bldg., Edmonton, Alberta. Meets first Tuesday of each month. October to May.

FACULTY OF RADIOLOGISTS

Honorary Secretary, Dr. C. J. Hodson, 47 Lincoln's Inn Fields, London, W.C.2, England. Annual meeting: Hammersmith Hospital and the Postgraduate Medical School, London, June 15-16, 1962.

SECTION OF RADIOLOGY OF THE ROYAL SOCIETY OF MEDICINE (CONFINED TO MEDICAL MEMBERS)

Meets third Friday each month at 4:45 p.m. at the Royal Society of Medicine, 1 Wimpole St., London, W. 1.

CANADIAN ASSOCIATION OF RADIOLOGISTS

Honorary Secretary, Dr. Robert G. Fraser, *Associate Honorary Secretary*, Dr. Jean-Louis Léger, 1555 Summerhill Ave., Montreal 25, Que. Annual meeting to be announced.

MONTREAL RADIOLOGICAL STUDY CLUB

Secretary, Dr. F. McConnell, 1650 Cedar Ave., Montreal, Quebec. Meets first Tuesday evening, October to April.

SECTION OF RADIOLOGY, CANADIAN MEDICAL ASSOCIATION

Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

SOCIÉTÉ CANADIENNE-FRANÇAISE D'ELECTRO-RADIOLOGIE MÉDICALE

General Secretary, Dr. Maurice Dufresne, 1560 Sherbrooke (East), Montreal, Canada. Meets third Saturday each month.

TORONTO RADIOLOGICAL SOCIETY

Secretary, Dr. Wallace M. Roy, St. Joseph's Hospital, 30 The Queensway, Toronto 3, Ontario. Meets second Monday of each month September through May.

COLLEGE OF RADIOLOGISTS OF AUSTRALIA

Honorary Secretary, Dr. E. A. Booth, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W., Australia.

SOUTH AMERICA

ASOCIACIÓN ARGENTINA DE RADIOLOGÍA

Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151, Córdoba, Argentina. Meetings held monthly.

ATENEO DE RADIOLOGIA

Secretary, Dr. Victor A. Añafios, Instituto de Radiología, Santa Fe 3100, Rosario, Argentina. Meets monthly on second and fourth Fridays at 7:00 p.m. in the Hospital Nacional del Centenario, Santa Fe 1300, Rosario.

COLÉGIO BRASILEIRO DE RADIOLOGIA

Secretary-General, Dr. Tede Eston de Eston, Caixa Postal 5984, São Paulo, Brazil.

SOCIEDAD ARGENTINA DE RADIOLOGÍA, JUNTA CENTRAL, BUENOS AIRES

Secretary, Dr. Edgardo O. Olcese, Santa Fé 1171, Buenos Aires. Meetings are held monthly.

SOCIEDAD BOLIVIANA DE RADIOLOGÍA

Secretary, Dr. Javier Prada Méndez, Casilla 1596, La Paz, Bolivia. Meets monthly. General assembly once every two years.

SOCIEDADE BRASILEIRA DE RADIOLOGIA

Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. General Assembly meets every two years in December.

SOCIEDADE BRASILEIRA DE RADIOTERAPIA

Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 p.m. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

SOCIEDAD CHILENA DE RADIOLOGÍA

Secretary, Dr. J. P. Velasco, Avenida Santa María 0410, Santiago, Chile. Meets fourth Friday of each month.

SOCIEDAD COLOMBIANA DE RADIOLOGIA

Secretary, Dr. Alberto Mejía Diazgranados, Carrera 13, No. 25-31, Apartado aéreo No. 5804, Bogotá, Colombia. Meets last Thursday of each month.

SOCIEDAD ECUATORIANA DE RADIOLOGÍA Y FISIOTERAPIA

Secretary, Dr. Publio Vargas P., Casilla 1242, Guayaquil, Ecuador.

SOCIEDAD PARAGUAYA DE RADIOLOGÍA

Secretary, Dr. Miguel González Addone, 15 de Agosto 322, Asunción, Paraguay.

SOCIEDAD PERUANA DE RADIOLOGIA

Secretary, Dr. Luis Pinillos Ganoza, Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

SOCIEDAD DE RADIOLOGIA DEL ATLANTICO

Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiología.

SOCIEDAD DE RADIOLOGÍA, CANCEROLOGÍA Y FÍSICA MÉDICA DEL URUGUAY

Secretary-General, Dr. Ernesto H. Cibils, Av. Agraciada 1464, piso 13, Montevideo, Uruguay.

SOCIEDADE DE RADIOLOGIA DE PERNAMBUCO

Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

SOCIEDAD DE ROENTGENOLOGIA Y MEDICINA NUCLEAR DE LA PROVINCIA DE CÓRDOBA

Secretary-General, Dr. Carlos A. Oulton, Santa Rosa 447, Córdoba, Argentina.

SOCIEDAD VENEZOLANA DE RADIOLOGÍA

Secretary-General, Dr. Rubén Merinfeld, Apartado No. 9362, Candelaria, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

CONTINENTAL EUROPE

ÖSTERREICHISCHE RÖNTGEN-GESELLSCHAFT

President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allgemeine Poliklinik.

SOCIÉTÉ BELGE DE RADIOLOGIE

General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets in February, March, May, June, October, November and December.

SOCIÉTÉ FRANÇAISE D'ELECTRORADIOLOGIE MÉDICALE

and its branches: SOCIÉTÉ DU SUD-OUEST, DU LITTORAL MÉDITERRANÉEN, DU CENTRE ET DU LYONNAIS, DU NORD, DE L'OUEST, DE L'EST, ET D'ALGER ET D'AFRIQUE DU NORD. Central Society meets third Monday of each month, except during July, August and September, rue de Seine 12, Paris.

Secretary-General, Dr. Ch. Proux, 9 rue Daru, Paris 8^e, France.

ČESKOSLOVENSKÁ SPOLEČNOST PRO ROENTGENOLOGII A RADIOLOGII

Secretary, Dr. Robert Poch, Praha 12, Šrobárova 50, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

DEUTSCHE RÖNTGENGESELLSCHAFT

Secretary, Professor Dr. med. H. Lossen, Universitäts-Röntgeninstitut, Lagenbeckstr. 1, Mainz, Germany. Annual meeting to be announced.

SOCIETÀ ITALIANA DI RADIOLOGIA MEDICA E DI MEDICINA NUCLEARE

Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

NEDERLANDSE VERENIGING VOOR ELECTROLOGIE EN RÖNTGENOLOGIE

Secretary, Dr. J. R. von Ronnen, Violonweg 14, den Haag, Netherlands.

SCANDINAVIAN ROENTGEN SOCIETIES

The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

SOCIEDAD ESPAÑOLA DE RADIOLOGÍA Y ELECTROLOGÍA MÉDICAS Y MEDICINA NUCLEAR

Secretary, Dr. D. Aureo Gutierrez Churruga, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

SCHWEIZERISCHE GESELLSCHAFT FÜR RADIOLOGIE UND NUKLEARMEDIZIN (SOCIÉTÉ SUISSE DE RADIOLOGIE ET DE MÉDECINE NUCLÉAIRE)

Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

INDIA

INDIAN RADIOLOGICAL ASSOCIATION

Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.



ABSTRACTS OF RADIOLOGICAL LITERATURE

INDEX TO ABSTRACTS

ROENTGEN DIAGNOSIS

NECK AND CHEST

- QUEREILHAC, H.: The esophagus and sigmoid aorta..... 623

ABDOMEN

- SANCHEZ, L. A.: Spiegel's hernia..... 623
BÜCKER, J.: Errors and misconceptions in the diagnosis of gastritis..... 623
GUGLIANTINI, P.: The oblique caudo-cranial position in the study of congenital hypertrophic pyloric stenosis..... 623
FONTAINE, R. *et al.*: Role of radiology in the pathology of Meckel's diverticulum..... 623
LEVENE, G.: Low temperature barium-water suspensions for roentgenologic examination of the colon..... 624
O'NEILL, P. B.: Gastrointestinal abnormalities in the collagen diseases..... 624
BOISOT, J. *et al.*: Radiologic diagnosis of cholesterosis..... 625

GYNECOLOGY AND OBSTETRICS

- LITTLE, H. M., JR. *et al.*: The use of gynecography in pelvic diagnosis..... 625
EPSTEIN, B. S.: Radiographic identification of arthrogryposis multiplex congenita in utero. 625

GENITOURINARY SYSTEM

- SIGGERS, R. L.: Early physiologic nephro-urography as a test of kidney function..... 626
BOYD, J. D., and MURDOCK, H. R., JR.: Urinary excretion of radiohippuran as a measure of renal function..... 626
MEADE, R. C., and SHY, C. M.: The evaluation of individual kidney function using radioiodhippurate sodium..... 626

- O'CONOR, V. J., JR., LIBRETTI, J. V., and GRAYHACK, J. T.: The early differential diagnosis of postoperative anuria using the radioactive renogram: an experimental study. 627
HALPERN, M., FINBY, N., and EVANS, J. A.: Percutaneous transfemoral renal arteriography in hypertension..... 628
STEINBERG, I., and MARSHALL, V. F.: Intravenous abdominal aortography in urologic diagnosis..... 628
BOHNE, A. W., URWILLER, R. D., and PANTOS, T. G.: Routine intravenous urograms prior to prostatectomy..... 629
BANKS, D. E., JR. *et al.*: Effects of intermittent irradiation in situ on renal homotransplantation..... 629
HUTCH, J. A.: Saccule formation at the ureterovesical junction in smooth walled bladders.. 629

SKELETAL SYSTEM

- LINSALATA, P., CAVARA, G., and DI MIZIO, V. I.: On Albers-Schönberg disease and its most frequent complications..... 630
GHIGO, M., and MAGRINI, M.: Osteo-periosteopathies secondary to tropical ulcers..... 630
KIM, J. P., and KHERA, S. A. K.: Polyostotic fibrous dysplasia associated with hyperthyroidism..... 630
RIEDERER, J.: A case of Pyle's congenital familial bone dysplasia (Pyle's disease).... 631
FUCILLA, I. S., and HAMANN, A.: Hodgkin's disease in bone..... 631
COVENTRY, M. B.: Some skeletal changes in the Ehlers-Danlos syndrome; a report of two cases..... 632
KELLY, P. J., JAMES, J. M., and PETERSON, L. F. A.: The effect of beryllium on bone; a morphological study of the progressive changes observed in rabbit bone..... 632



ROENTGEN DIAGNOSIS

NECK AND CHEST

QUEREILHAC, HECTOR. Esofago y aorta sigmoidea. (The esophagus and sigmoid aorta.) *Prensa méd. argent.*, Mar. 10, 1961, 48, 623-629.

Advanced sclerotic changes in the thoracic portion of the aorta produce three basic configurations: (a) widening of the radius of the aortic arch; (b) sigmoid curvature of the descending portion; and (c) widening of the entire aorta.

Four cases are reported in which the sclerotic changes have caused alteration in the configuration of the barium-filled esophagus.—*M. M. Friedman, M.D.*

ABDOMEN

SANCHEZ, L. ARRIETA. Hernia de Spiegel. (Spiegel's hernia.) *Radiología, Panamá*, June, 1961, 11, 110-113. (Address: Radiólogo, Hosp. Santo Tomás, Panamá.)

Hernia of the linea semilunaris (Spiegel's hernia) is a common type of spontaneous ventral hernia. Predisposing factors are ptosis, obesity, muscular atrophy, emaciation, ascites and severe muscular stress. The relationship of the lateral branch of the deep inferior epigastric artery which traverses one of the defects encountered in this region has also been considered to be a contributory factor in these hernias. Before operation, it is impossible clinically to distinguish a hernia of the linea semilunaris from a direct inguinal hernia.

In a case described by the author, a reducible mass was found in the left lateral inferior portion of the abdomen. Fluoroscopically, barium was found to be retained in a U-shaped loop in the sigmoid corresponding to the mass in the abdominal wall. At operation, a 5 cm. defect was found in the abdominal wall at the line of the linea semilunaris. The hernia was reduced without difficulty.—*M. M. Friedman, M.D.*

BÜCKER, J. Errors and misconceptions in the diagnosis of gastritis. *German Med. Monthly*, July, 1961, 6, 223-226. (From: The General Hospital, Heidberg, Hamburg, Germany.)

The roentgenologic diagnosis of gastritis must be made only when there is adherence to rigid criteria. Too frequently the diagnosis is based on changes in mucosal relief which are within the range of normal. The appearance of gastritis, including the chronic type, depends on the presence of inflammatory edema which involves the mucosal folds, submucosa, muscularis and subserous layers. It is important to distinguish between the variable, elastic, easily deformed folds of varying size in the normal stomach

and the immobile, coarsely deformed, stiff and thickened relief pattern of the stomach involved by gastritis. The presence of erosions and pseudopolyposis is added roentgenologic evidence of gastritis. Inflammatory edema may cause the gastric wall to become four to six times normal thickness and the stomach to increase strikingly in weight. Following resection the distribution of the fluid changes markedly with resulting reduction in the height of the folds.

These artifactual changes should be appreciated by one who is attempting to correlate roentgenologic findings with anatomic material.—*David Morse, M.D.*

GUGLIANTINI, P. Utilità delle incidenze oblique caudo-craniali nello studio radiologico della stenosi congenita ipertrofica del piloro. (The oblique caudo-cranial position in the study of congenital hypertrophic pyloric stenosis.) *Ann. radiol. diag.*, 1961, 34, 56-69. (From: Reparto di Radiologia, Ospedale Pediatrico del Bambino Gesù, Rome, Italy.)

In a previous communication, the author described the use of this position to demonstrate changes in the newborn and in infants afflicted with congenital hypertrophic pyloric stenosis.

Because in this age group the stomach lies in a horizontal position and usually is distended, the pyloric canal and duodenal bulb lie posterior to the antral portion of the stomach. Utilizing the conventional position with the central beam directed perpendicular to this area, the overlapping of structures on roentgenograms makes a definite diagnosis either difficult or impossible. However, if the central beam is aimed in an oblique caudad-cephalic direction at an angle of 20 to 25 degrees, the antral portion of the stomach, the pyloric canal and duodenal bulb are so situated on roentgenograms that they can be clearly visualized and evaluated.

The article includes a report of 5 cases, all confirmed at surgery, of congenital hypertrophic pyloric stenosis. Each case is illustrated by reproductions of two roentgenograms, one taken by the conventional method and the other using the technique advocated by the author. These illustrations are convincing.

Since a definite diagnosis in these cases can only be made by the demonstration on roentgenograms of an elongated and narrowed pyloric canal, this method of examination should increase our percentage of correct diagnosis.—*Peter E. Russo, M.D.*

FONTAINE, R., WARTER, P., WAHL, R., and WEILL, F. (Strasbourg, France.) Apport de la radiologie dans la pathologie du diverticule de Meckel. (Role of radiology in the pathology of Meckel's diverticulum.) *J. de radiol., d'électrol. et de méd. nucléaire*, June-July, 1961, 42, 327-333.

Meckel's diverticulum represents a remnant of the

umbilical sac which in the embryo communicates between the umbilicus and the primitive intestine. Normally this atrophies and is transformed into a cord-like structure towards the seventh week. Usually these remnants disappear towards the end of the third month of the intra-uterine life.

A disturbance in this process of evolution and development may result in fistulous formation, intestinal atresia, or a true Meckel's diverticulum. The latter occurs within the last 1 meter (40 inches) of the ileum and is located on the antimesenteric border of the small intestine. Its histologic structure is identical with that of the small intestine. At times, heterotopic mucosal inclusions may occur, of gastric, duodenal or of pancreatic tissue.

It has been reported that from 2 to 4 per cent of individuals may retain a Meckel's diverticulum. Thus in a large number of patients there is the possibility of their coming to the surgeon because of abdominal conditions resulting from Meckel's diverticulum. These may be caused by occlusions, may be due to inflammation, or simple diverticulitis simulating appendicitis, or to perforation and hemorrhage as occurs with peptic ulcer. Meckel's diverticula also may herniate.

Rarely tumors may develop in the wall of the diverticulum. They may be benign—lipoma, leiomyoma, fibroma and hamartoma; or malignant—epithelioma, carcinoid and sarcoma. This multiplicity of pathologic possibilities presents a serious challenge in the roentgenologic diagnosis.

In acute complications the roentgen findings may be of little assistance. However, in chronic or subacute conditions the radiologist may be able to help by demonstrating the presence, location and extent of a Meckel's diverticulum.

In an attempt to visualize the diverticulum, the authors use orally administered barium during a small intestinal study. They do not recommend the barium enema examination in such cases.

The authors present their findings in 13 cases in which the roentgen diagnosis was made. Where the Meckel's diverticulum was demonstrated, it seemed to offer a satisfactory explanation of the abdominal condition for which the patient was being examined.

Seven sketches and diagrams with reproductions of roentgenograms accompany this article.—*William H. Shehadi, M.D.*

LEVENE, GEORGE. Low temperature barium-water suspensions for roentgenologic examination of the colon. *Radiology*, July, 1961, 77, 117-118. (Address: Massachusetts Memorial Hospitals, Boston 18, Mass.)

For a number of years the author has been employing water at a temperature of 41° F. in preparing the barium-water suspension for barium enema examinations. This low temperature suspension has been used in several thousand cases. The author

claims that this suspension possesses certain advantages in both the routine barium enema and the double-contrast studies.

These advantages are listed as follows: (1) there is less hyperemia of the colon and therefore less irritability; (2) the mild anesthetic effect of the colder suspension raises the threshold of excitability. This and the decreased hyperemia result in better and more comfortable retention of the enema; (3) tonic contraction of the anal sphincter is stimulated, contributing to the ease of retention; (4) relaxation of the colon, in accordance with the law of reciprocal innervation, permits more rapid flow of the enema with less tenesmus and discomfort to the patient; and (5) there is reduction of the tendency to bubble formation of the air or carbon dioxide used in double-contrast examinations, since all gases are more soluble in cold than in warm liquids.—*Donald N. Dysart, M.D.*

O'NEILL, PHILIP B. Gastrointestinal abnormalities in the collagen diseases. *Am. J. Digest. Dis.*, Nov., 1961, 6, 1069-1083. (From: Marquette University Medical School, Milwaukee, Wis.)

Sixty-one patients were selected with the diagnosis of collagen diseases confirmed by clinical course, biopsy or necropsy, or positive L.E. cell preparation. These were analyzed with emphasis on gastrointestinal abnormalities.

Twenty-eight patients had systemic lupus erythematosus, 17 of whom exhibited prominent gastrointestinal features. Polyarteritis was the second most common, with 10 of 14 patients having gastrointestinal findings. Ten of the 12 patients with scleroderma and 4 of the 6 with dermatomyositis had major symptoms and signs referable to the alimentary tract.

Dysphagia, usually intermittent, was noted in all 4 conditions. The etiology was frequently obscure. Buccal and esophageal mucosal ulceration and pharyngeal edema were encountered in lupus erythematosus. The swallowing difficulty in polyarteritis has been ascribed to necrotizing arteritis in the muscular arteries of the esophagus. In scleroderma dysphagia has resulted from constrictive changes in the lower esophagus, diminished motility at the cardia and dilatation with retardation of passage. Intraluminal pressure studies have demonstrated the lack of tone in the lower one-third of the esophagus causing the patient to be dependent on gravity for transesophageal passage. Esophageal luminal constriction was also encountered in dermatomyositis.

All 61 patients had periodic and usually disabling abdominal pain. Intermittent nausea and vomiting were likewise present.

The roentgenologic findings varied. Dilatation of the cervical esophagus was observed in 1 patient with dermatomyositis. Three lupus erythematosus pa-

tients had prolonged and pronounced colon spasm. Dilatation and lack of esophageal tone were noted in 2 women with scleroderma. Dilatation and diminished contractility of the proximal small bowel were also noted. Scleroderma patients in the supine position frequently had marked esophageal retention of barium but this rapidly traversed the cardia and entered the stomach when the patient assumed the erect position.—*David Morse, M.D.*

BOISOT, J., LAGARDE, CL., FONTAYNE, A., and LAURENS, G. (Bordeaux, France.) Le diagnostic radiologique de la cholestérolise. (Radiologic diagnosis of cholesterolosis.) *J. de radiol., d'électrol. et de méd. nucléaire*, June-July, 1961, 42, 334-342.

Cholesterolosis—the term introduced by Mentzel in 1925—refers to a pathologic condition of the gallbladder consisting of a high cholesterol deposit.

The condition has been well known to pathologists but the work of Jutras and his co-workers have stressed this entity to the radiologists, as reported by them in the recent radiologic literature. Cholesterolosis may be diffuse involving practically the entire gallbladder wall (strawberry gallbladder), or it may be localized assuming a polypoid appearance. These polyps may be single or multiple, sessile or pedunculated, sharply defined or irregular.

The diffuse form is manifested by an irregular moth-eaten appearance of the entire gallbladder wall, whereas the polypoid form presents well defined fixed defects.

Accompanying these pathologic changes there are characteristic functional disturbances of roentgenologic significance. There is hyperconcentration as evidenced by increased density of the gallbladder and there is also hyperexcitability or hypermotility as evidenced by rapid and almost complete emptying within twenty minutes. The pathologic basis for this is the increased proliferation of the mucosal surface as well as of the nerve element, manifested by a certain degree of neuromatosis.

The roentgenologic criteria are based on the constancy of the defects which often are best seen on the delayed or postevacuation gallbladder roentgenograms, on the hyperconcentration of the contrast material and on the rapid evacuation of the gallbladder.

The differential diagnosis includes identification of intestinal gas, nonopaque calculi and polyps and fixed defects due to other tumorous conditions in the gallbladder wall.

The authors based their report on 17 cases observed during the study of 701 oral cholecystographies through a three year period (1958 to 1960 inclusive).

Fourteen excellent reproductions of roentgenograms and one sketch accompany this article.—*William H. Shehadi, M.D.*

GYNECOLOGY AND OBSTETRICS

LITTLE, HARRY M., JR., HUTCHINSON, JOHN F., RICHEY, L. E., and SCHREIBER, MELVIN. The use of gynecography in pelvic diagnosis. *South. M. J.*, July, 1961, 54, 715-720. (From: The Departments of Obstetrics and Gynecology, and of Radiology, University of Texas Medical Branch, Galveston, Tex.)

The use of pneumoperitoneum combined with roentgenography for visualizing abdominal tumors was first reported in 1912. Hysterosalpingography was described by Cary in 1914 using collargol, a silver salt. In 1927 Stein reported the combined use of hysterosalpingography and pneumoperitoneum calling the procedure gynecography. Its greatest use is in the obese patient, the rigid uncooperative patient, children and others when only a rectal examination can be done. Hysterosalpingography is contraindicated in pregnancy, uterine bleeding, purulent cervical or uterine discharge, acute or subacute pelvic inflammatory disease, shock, localized or diffuse peritonitis, large tumor masses filling the pelvis, and in elderly and poor risk cardiac patients. The transabdominal route for pneumoperitoneum is contraindicated in shock, peritonitis, large tumor masses filling the pelvis and in elderly or poor risk cardiac patients. Cul de sac puncture for pneumoperitoneum has the same contraindications. The complications of pneumoperitoneum are transient: shoulder pain, nausea, vomiting, vertigo and abdominal pain. The complications of hysterosalpingography are rupture of the uterus and tubes, venous intravasation of contrast medium with occasional pulmonary embolism, transportation of infection or malignant cells into the peritoneal cavity, and allergic reaction to the contrast agent. Fortunately these are rare. For the transabdominal route an 18 gauge needle is inserted into the left abdomen below the umbilicus. Under 30-40 mm. Hg pressure, 1,000-1,500 cc. of CO₂ is injected. The transuterine technique is performed in the same manner as the Rubin tubal patency test. The cul de sac puncture technique is described in the gynecologic literature. Following the introduction of air the patient is placed prone in 30 degrees Trendelenburg position. The roentgenographic tube is angled 15 degrees toward the feet. For complete gynecography, contrast material is injected through a preplaced cannula.

Because this technique was utilized patients were spared laparotomy, culdoscopy or examination under anesthesia. It can be employed in the search for recurrent tumor following hysterectomy and salpingo-oophorectomy.—*David Morse, M.D.*

EPSTEIN, BERNARD S. Radiographic identification of arthrogryposis multiplex congenita in utero. *Radiology*, July, 1961, 77, 108-110. (Address: The Long Island Jewish Hospital, New Hyde Park, N. Y.)

Arthrogryposis multiplex congenita is a condition characterized by varying degrees of joint contractures attributed to the effects of a dystrophic muscular disorder of unknown origin. Joint mobility is interfered with due to increased periarticular fibrous tissue. While the bones are not involved, the skin and subcutaneous tissues are sometimes affected. Associated congenital malformations of the skull and spine, polydactyly, and hip dislocation are frequent concomitants. A hereditary factor may exist.

Slender extremities with prominent joints fixed in flexion, extension, or both are characteristically seen in the newborn infant. This abnormal fixation and attitude of the extremities may be apparent on pelvimetric or abdominal roentgenograms and these findings, if present on other roentgenograms obtained at a later date, should provide a diagnostic clue as to the presence of this entity.

The author presents 2 cases in which roentgenograms obtained prior to delivery showed the abnormal position of the lower extremities. In both instances, however, the significance of these observations was not recognized prior to delivery. A suggestion is made that if prepartum abdominal roentgenograms show hyperextension of the legs on the thighs and flexion of the thighs on the abdomen, another roentgenogram a day later after manipulation of the maternal abdomen should be made to see if the limbs change position. If there is no change in position, abnormal fixation may be present, leading to the suggestion that arthrogryposis multiplex congenita should be considered.—*Donald N. Dysart, M.D.*

GENITOURINARY SYSTEM

SIGGERS, RICHARD L. Early physiologic nephrography as a test of kidney function. *Radiology*, Sept., 1961, 77, 452-457. (Address: Long Beach Veterans Hospital, Long Beach, Calif.)

The author, believing that intravenous pyelography, if performed soon enough after injection of contrast material, would demonstrate disparity between the function of one kidney and the other, instituted a program in his department to show this. The procedure is as follows: a preliminary roentgenogram of the kidney regions is obtained prior to intravenous pyelography. Then 30 cc. of 50 per cent hypaque sodium is injected intravenously as rapidly as possible. The first pyelogram is obtained one minute after the beginning of the injection. A second film is exposed one minute after the first, and a third, one minute after the second. Routine five-, ten-, fifteen-, and twenty-minute morphologic pyelograms are then obtained.

The one-minute film usually shows a nephrogram, the kidney shadows being slightly denser than on the preliminary film. The two-minute film, in a normal patient, shows a fully apparent nephrogram. The

three-minute film, in a normal normotensive patient, shows beginning bilateral calyceal delineation. In patients with essential hypertension, the calyces are often seen on the two-minute film because the medium apparently traverses the kidney more rapidly due to the renal arterial blood pressure. Those patients with hypertension due to arterial insufficiency of one kidney, as in a Goldblatt kidney, will show a difference in the rapidity of appearance of the calyceal phase in the two kidneys.

The clinical reports on two cases are presented. Each of these patients had hypertension and showed on their intravenous pyelographic studies a differential excretion of contrast material on the two-, and three-minute films. Other tests demonstrated differential function between the two kidneys and aortograms showed unilateral renal artery constriction. Following subsequent surgery to remove the cause of the constriction in the renal arteries the blood pressure in each patient returned to normal.—*Donald N. Dysart, M.D.*

BOYD, JULIAN D., and MURDOCK, HAROLD R., JR. Urinary excretion of radiohippuran as a measure of renal function. *J. Urol.*, Sept., 1961, 86, 294-295. (From: The Veterans Administration Hospital, Huntington 1, W. Va.)

This report deals with the findings from tests employing radiohippuran in the study of 88 patients. In addition to radiohippuran renograms, the authors have determined the percentage excretion at intervals of 20 minutes and 90 minutes after injection. This determination is made in a well counter and a third figure which represents proportion of the aggregate 90 minute excretion which occurred during the first 20 minutes has also been calculated.

The results show that in normal individuals, there is at least 55 per cent excretion of the injected dose at the end of 20 minutes, and 80 per cent aggregate excretion in 90 minutes. The 20 minute excretion amounted to approximately 70 per cent of the aggregate. Patients with renal or vascular disease showed diminished outputs of radiohippuran which seemed to be in accord with the severity of the disease process.

The test is fundamentally a blood clearance test in association with radiorenography.—*George W. Chamberlin, M.D.*

MEADE, ROBERT C., and SHY, CARL M. The evaluation of individual kidney function using radioiodohippurate sodium. *J. Urol.*, July, 1961, 86, 163-170. (From: The Radioisotope Service of the Wood Veterans Administration Center and the Marquette University School of Medicine, Milwaukee, Wis.)

Hippuran, the sodium salt of ortho-iodohippuric acid, is rapidly removed from the blood stream by

the kidney and is almost completely extracted in one passage through the renal tubules. It has been shown to have practically no concentration in the liver.

In this evaluation, the authors use I^{131} in the ortho-iodo position of hippuran in a study which illustrates the range of normal renogram tracings.

The subjects examined were clinically free of hypertension and had no known renal disease. They were nonfasting and were given 500 cc. of water fifteen minutes prior to the test. These patients were in a sitting position, leaning forward against a chair back. The dual detection system equipped with $1\frac{1}{2}$ inch sodium iodide crystals with dual recorders and wide collimation was utilized. The time constant at the count rate meter was set at 1.5 seconds and the sensitivity was set at 10,000 counts per minute full scale. A localizing dose of .03 μ c/kg. of hippuran was injected intravenously and the detectors were placed against the back without pressure at the area of maximum activity posterior to each kidney. The count rate meters were then switched to a sensitivity of 30,000 cpm full scale, the time constant remained at 1.5 seconds, and the paper speed at 30 cm. per hour. The renogram dose of 0.3 μ c/kg. was then injected intravenously and the tracing continued for twenty minutes or longer. Thirty minutes after injection of the dose, a voided urine specimen was obtained and the per cent excretion calculated. Suprapubic counts were made before and after voiding to detect any urinary retention.

The typical normal renogram shows three segments: the initial rise which represents the radioactivity of the blood in the kidney and surrounding tissues, a more gradual secondary rise which results from tubular secretion of hippuran to a maximum level which occurs two to four minutes after injection, and a third segment which is a moderately rapid fall indicating the elimination of radioactive urine from the kidney. The amplitude of the curve of the right renogram is slightly higher in normal patients than that of the left renogram. This has been attributed to the increased volume of blood in the liver and perirenal tissues on the right as compared to the left. Less than 2/10 of 1 per cent of the isotope was recovered from the bile of a patient in twenty-four hours and over 98 per cent was excreted in the urine indicating that hippuran is completely cleared from the blood by the kidneys. Thirty minute excretion was 67.7 per cent with a plus or minus variation of approximately 6 per cent in the normal patients. The excretory slope of the renogram tracing did not correlate well with the thirty minute excretion, and the addition of a hippuric acid "load" equal to more than 10,000 times the hippuran dose did not alter the thirty minute excretion in normal patients. This thirty minute excretion appears to be a very excellent screening test since there is virtually no counting error. Normal patients studied several months apart had less than 5 per cent variation in a majority of cases.

Renograms in patients with normal kidney function may be influenced by pain and apprehension. Factors of hydration versus dehydration and extension of the spine versus the prone position have been evaluated carefully by the authors. It is suggested that when an abnormality is noted on the upright renogram a prone renogram should be done to further evaluate the significance of this finding.

Seven composite charts illustrate the above investigations and the conclusions of the authors.—George W. Chamberlin, M.D.

O'CONOR, VINCENT J., JR., LIBRETTI, JOSEPH V., and GRAYHACK, JOHN T. The early differential diagnosis of postoperative anuria using the radioactive renogram: an experimental study. *J. Urol.*, Aug., 1961, 86; 276-279. (From: The Department of Urology, Northwestern University Medical School, Chicago, Ill.)

This is an experimental study using 3 groups of animals in an attempt to find a better method for the early diagnosis of postoperative oliguria or anuria.

One group of 13 dogs was subjected to bilateral lower ureteral ligation. Five hundred cubic centimeters of 5 per cent dextrose solution were administered during this operative procedure, and radioactive renograms were performed initially and daily thereafter as long as the dogs survived, which ranged from two to five days. Autopsies and gross and microscopic studies were then carried out.

Sixteen dogs in the second group were subjected to a four hour period of bilateral renal artery and vein occlusion. Five hundred cubic centimeters of 5 per cent dextrose solution were given intravenously during the operation, and radioisotope renograms were performed daily over a period of from sixteen hours to seventy-two hours.

The third group consisted of 11 dogs which were subjected to intraperitoneal dialysis over a two hour period with 10 per cent dextrose in water to produce an acute dehydration. These animals were studied by radioactive renograms postoperatively after dehydration and again after rehydration with isotonic saline solution or Ringer's solution. Two of the animals were allowed to die of acute dehydration.

The results show that all animals in group 1 were totally anuric. Radioisotope renograms within the first forty-eight hours were characteristic of acute ureteral obstruction. Following the initial vascular spike, there was a progressive rise demonstrating continued accumulation of the radioisotope in the area of the kidney with no evidence of excretion. Subsequent tracings showed a progressive loss of tubular function as evidenced by flattening of the secretory or accumulation phase and an apparent gradual reduction of the vascular spike. Between forty-eight and seventy-two hours, the renogram tracing became indistinguishable from that of the

nonfunctioning kidney, and no change could be effected in these tracings at any time by hydration.

All animals in group 2 were severely oliguric, showed progressive azotemia, and were dead by the third postoperative day. Serial and renal biopsies, as well as autopsy specimens, showed changes consistent with acute tubular necrosis. The radioactive renograms in this group showed a low vascular spike, a flat accumulation phase and essentially no clearance. Subsequent to the first twenty-four hours, serial tracings showed a similar pattern with a gradual reduction in the vascular spike. These tracings were easily distinguishable from the obstructed group during the first forty-eight hours after complete ureteral obstruction, but could not be distinguished from the group 1 renograms after forty-eight hours.

The renograms obtained on 10 of the 11 acutely dehydrated dogs were similar to those in the bilaterally obstructed group. Following the vascular spike, there was an acute rise compatible with tubular function and a progressive slow rise signifying lack of excretion. Upon rehydration the rapid clearance of the radioisotope became evident in all animals after approximately one-third of the calculated fluid loss had been infused.

This study suggests that the radioisotope renogram may be of clinical value in the early differentiation of ureteral obstruction from the other causes of acute urinary suppression in the postoperative patient.—*George W. Chamberlin, M.D.*

HALPERN, MORDECAI, FINBY, NATHANIEL, and EVANS, JOHN A. Percutaneous transfemoral renal arteriography in hypertension. *Radiology*, July, 1961, 77, 25-33. (Address: M. Halpern, 525 East 68th St., New York 21, N. Y.)

Renal arteriography finds its most important application in the study of renal hypertension. Of the various methods available for opacification of the renal arterial system, the modified Seldinger technique of percutaneous transfemoral retrograde arteriography is a safe, simple and precise method to demonstrate the anatomy and pathology of the renal arteries and their intrarenal branches. The authors report the results in the first 41 cases studied following their adoption of the above technique.

The indications for renal arteriography as utilized in the study are: hypertension in a patient under the age of fifty with no other demonstrable cause; development of malignant hypertension or sudden development of hypertension at any age; and hypertension that first appears or increases following an episode of flank pain or following abdominal trauma. In addition, accurate visualization of the renal arteries is mandatory when differential renal excretion studies reveal more than 15 per cent decrease in the excretion of sodium and/or a 50 per cent drop in water output.

The results of this selective study reveal a variety of remedial lesions. A simple pathologic classification is as follows: (1) fibromuscular hyperplasia with associated segmental stenosis; (2) arteriosclerotic plaques with or without poststenotic dilatation; (3) complete occlusion of a renal artery with atrophy of the kidney; (4) thrombosis or embolism; (5) a miscellaneous group including chronic pyelonephritis, diminished function and reduced vascularity in an atrophic kidney, and a partially calcified renal artery aneurysm.

The authors advise a selection of hypertensive patients for study, based on the stated indications. In this reported series, 49 per cent of these patients showed a variety of lesions, while 24 per cent of those patients with remedial lesions were below forty years of age.

The authors, in conclusion, draw special attention to one of their patients with clinical evidence of hyperaldosteronism who continued to exhibit hypertension after total adrenalectomy. Subsequent renal arteriography demonstrated a "coarctation" of the left renal artery and the patient became normotensive after a left nephrectomy. As a result, they recommend that patients, with aldosteronism and perhaps even pheochromocytoma, have percutaneous transfemoral renal arteriography before surgery.—*Edward B. Best, M.D.*

STEINBERG, ISRAEL, and MARSHALL, VICTOR F. Intravenous abdominal aortography in urologic diagnosis. *J. Urol.*, Oct., 1961, 86, 456-469. (From: The Departments of Radiology and Surgery (Urology), The New York Hospital—Cornell Medical Center, and the James Buchanan Brady Foundation of The New York Hospital, New York 21, N. Y.)

The authors present their experience with the intravenous method of opacification of the renal blood supply, aorta and iliac vessels in a series of over 400 consecutive patients with various diseases. Their technique consists of the use of 90 per cent hypaque injected rapidly and simultaneously into the right and left antecubital vein. The technique is exacting and requires good cooperation from the patient.

The intravenous method is an alternate procedure which may supplement direct aortography or which may replace it when the latter is contraindicated. It offers the advantage of a wide view of the abdominal and iliac vascular system and aortograms may be obtained of other body areas if desired.

The studies thus far indicate that most of the gross abnormalities of major vessels within the abdomen had been revealed by this technique. The procedure is not without certain dangers. Extravasation of the contrast medium at the site of injection may occur in spite of proper precaution. At the time of publication of this article, 2 patients of the 400 died of pulmonary edema as a result of the study.

Sixteen composite illustrations are presented to

show the various lesions which may be demonstrable by this diagnostic method.—*George W. Chamberlin, M.D.*

BOHNE, A. W., URWILLER, R. D., and PANTOS, T. G. Routine intravenous urograms prior to prostatectomy. *J. Urol.*, July, 1961, 86, 171-172. (From: The Division of Urology, Henry Ford Hospital, Detroit 2, Mich.)

This is a short article which includes a statistical study of 500 patients whose intravenous pyelograms were chosen because their medical complaints consisted entirely of symptoms referable to prostatism with no other genitourinary abnormalities. In all of these instances, the diagnosis of benign prostatic hypertrophy had been proven by microscopic section. Of the 500 routine intravenous urograms, 39 or 7.8 per cent demonstrated renal abnormalities; hydro-nephrosis was present in 15; renal calculi in 12; and renal neoplasm in 10. One case showed polycystic disease and in 1 case a horseshoe kidney was diagnosed.

In view of the fact that the statistics show a mortality of only .0008 per cent from the diagnostic intravenous urographic study and in consideration of the important renal abnormalities which may be found on the intravenous urograms in this group of patients, the authors recommend routine intravenous urography prior to prostatectomy.—*George W. Chamberlin, M.D.*

BANKS, DUANE E., JR., AUBURN, RICHARD P., HUBAY, CHARLES A., and PERSKY, LESTER. Effects of intermittent irradiation in situ on renal homotransplantation. *J. Urol.*, Aug., 1961, 86, 181-184. (From: The Department of Surgery, Western Reserve University School of Medicine and the University Hospitals of Cleveland, Cleveland, Ohio.)

The rejection mechanism which prevents homotransplantation of tissues is generally regarded by investigators in this field to be due to an actively acquired immunity. The antigenic substance has been shown to be in the nuclear fraction, and the nature of this material is now thought to be a carbohydrate-protein complex. The current concept is that these amino acid-polysaccharide complexes are transported to the regional lymph nodes where cellular antibodies are formed which are then carried back to the graft via the blood stream and initiate the rejection of the transplant.

In an attempt to alter the host resistance to a homograft, the authors delivered intermittent irradiation to the graft site.

Two series of adult dogs of both sexes were divided equally into 10 animals each. Following the transplantation of a kidney into the neck of the animals in group 1, irradiation was given in daily increments of 100 r for an average total dose of 770 r over the

homotransplant. The radiation had a quality corresponding to 1.2 mm. of copper half value layer. In the second group of animals, the control set, the animals were anesthetized each day similarly to those which had been treated with radiation but no radiation was received by this group.

The homografts were considered as rejected when hematuria, anuria, or swelling occurred. The animals were then sacrificed, the kidneys removed, fixed and studied microscopically.

The results revealed that the 10 dogs receiving irradiation to the homograft showed a functional survival of the transplanted kidney of 9.1 days, whereas in the nonirradiated dogs the average survival of the transplanted kidney was 9.3 days. Grossly, the kidneys of both groups were similar. The grafted organs were uniformly enlarged with edematous, hemorrhagic, and bulging medullae. On microscopic examination, the appearance was similar in the two groups. There was evidence of pyelonephritis as well as diffuse round cell infiltration, tubular necrosis, and vascular thrombosis. The failure of intermittent irradiation suggests that the cells which carry the antibody to the homograft probably arrive continuously and need less than 24 hours to initiate the changes leading to rejection.—*George W. Chamberlin, M.D.*

HUTCH, JOHN A. Saccule formation at the ureterovesical junction in smooth walled bladders. *J. Urol.*, Oct., 1961, 86, 390-399. (Address: 2100 Monument Boulevard, Pleasant Hill, Calif.)

Saccule formation in patients with vesical neck obstruction and heavily trabeculated bladders has been recognized for many years. In this type of bladder, these lesions are commonly associated with ureteral reflux. In recent studies, similar saccule formation has been identified in smooth bladders which may or may not have vesical neck obstruction. These saccules have evaded recognition in the usual intravenous urograms, cystograms, and post-voiding bladder roentgenograms. They are difficult to recognize because they are intermittent and are seen only during the voiding period. Their demonstration depends upon multiple serial roentgenograms using rapid roentgenographic techniques or cine roentgenography during the voiding act. Twenty-eight of 74 patients studied in this way have shown ureteral reflux associated with saccule formation.

In this article, the anatomy of the ureterovesical junction is reviewed, the pathology and pathogenesis of the saccule are described, and the clinical significance of this lesion is discussed. The saccule proves to be a herniation of the vesical mucosa between the roof of the intravesical ureter and the roof of the ureteral hiatus. It is possible that this occurs in association with congenitally deficient bladder musculature. Differences between the saccule which forms in the smooth walled bladder and the one which

forms in the trabeculated bladder are discussed and an explanation is given for the relationship between ureteral reflux and saccule formation.

The author includes illustrations of 13 cases of saccule formation in smooth walled bladders and 2 figures showing the pathologic anatomy at the ureterovesical junction.—*George W. Chamberlin, M.D.*

SKELETAL SYSTEM

LINSALATA, P., CAVARA, G., and DI MIZIO, V. I. Sulla malattia di Albers-Schönberg e le sue più frequenti complicanze. (On Albers-Schönberg disease and its most frequent complications.) *Ann. radiol. diag.*, 1961, 34, 105-122. (From: Istituto di Radiologia, Ospedale Maggiore di Bologna, Bologna, Italy.)

The authors believe that about 200 cases of this rare disease have been reported in the world literature.

The extreme variability of this disease is discussed in relation to its period of onset and clinical manifestations. The etiology and pathogenesis still remain unknown. Although the typical triad is sclerosis of the skeleton, fragility of bones, and a secondary anemia, the clinical symptoms vary considerably. The diagnosis may not be made in certain cases until the patient sustains a fracture.

The main purpose of this article is to discuss the most common complications of these cases which survive for many years; *i.e.*, fractures, osteomyelitis, disturbance of vision, and hepatosplenomegaly. The case reported by the authors had all of these complications except the disturbance in vision.

The case is that of a thirty-three year old white female, married, and mother of 3 apparently healthy children. Her father, mother, and several sisters and brothers who were all examined were found to be normal except one sister who suffered recurrent infections of the mandible after extraction of a tooth. She was not available for examination since she had moved out of the country.

Since the age of eleven, the patient had suffered from an unexplained anemia which responded well to medical treatment. Several years later she was again treated for anemia, generalized lymphadenopathy and enlarged spleen which again responded well to treatment. At the age of thirty, the patient broke her arm following an injury. Roentgenograms revealed not only a fracture of the humerus but extreme eburnation of the entire bone. Skeletal studies disclosed similar involvement of all of the bones of the body and a diagnosis of Albers-Schönberg disease was made. The fracture healed without any difficulty. About a year later a carious tooth was extracted. Swelling of the mandible, abscess formation, and infection of the mandible developed which became resistant to any form of treatment.

The authors point out that the fragility of bones in

this disease is due to changes which weaken these structures. Susceptibility to infection is attributed to circulatory disturbances which result from these changes in the bones.

This is an excellent case report of a patient with osteopetrosis which apparently developed rather late in adolescence. The patient has survived for many years with anemia, asthenia, splenomegaly, and enlarged lymph nodes. Although the skeleton revealed very extensive bone disease, the fracture sustained after an injury led to the correct diagnosis.—*Peter E. Russo, M.D.*

GHIGO, M., and MAGRINI, M. Osteo-periostio-patie da ulcere tropicali. (Osteo-periosteopathies secondary to tropical ulcers.) *Radiol. med.*, Aug., 1961, 47, 719-727. (Address: Dott. Mario Ghigo, Via Leonardo da Vinci 8, Alassio (Savona), Italy.)

The 5 cases presented were studied by the senior author in the Department of Radiology of the Ahmed First Hospital of Hodeidah (Yemen). About 100 patients affected by tropical ulcers were examined and about 20 per cent of the cases presented bone lesions in correspondence with or near the skin lesions.

In almost all cases the lesions were in the leg and more frequently in the middle third of the anterior aspect. In order of frequency the other areas affected were the distal third of the lower leg and the foot in the dorso-lateral aspect.

Generally the time elapsing between the appearance of the tropical ulcer and the beginning of the bone changes was about a year.

The roentgen findings were characterized by a chronic osteitis and periosteitis secondary to a prolonged inflammatory process produced by the causative agents of the tropical ulcer (*Bacillus fusiformis* or *hastilis* [Seitz] and *Spirochaeta vincentii* or *schaudini*). The bone lesions were mainly localized in the periosteum and partially in the adjacent cortex. The limit between the periosteal proliferation and the cortical changes could not very frequently be determined. At times the cortex was thinned out and showed through the thickened periosteum with a saw-like appearance. Very rare were sequestra of bone, which, when present, were found only in the cortex, and usually were quite small. The bone marrow was not involved, except for occasional areas of sclerosis. In a few young patients there were deformities of the tibia and fibula: normally a bowing of the bones, secondary to weight bearing in the affected bones during childhood.—*A. F. Govoni, M.D.*

KIM, JOHN P., and KHERA, SHAMSHER A. K. Polyostotic fibrous dysplasia associated with hyperthyroidism. *J. Bone & Joint Surg.*, Sept., 1961, 43-A, 897-904. (From: Services

of Orthopaedics and Paediatrics, Regina General Hospital, Regina, Sask., Canada.)

The authors report the case of a ten year old boy with extensive segmental involvement of the skeleton with polyostotic fibrous dysplasia, multiple fractures, thyrotoxicosis, and a hypoplastic left testicle. This brings the number of such cases reported in the literature to 8.

Endocrine dysfunction is frequently associated with polyostotic fibrous dysplasia. Thyroid dysfunction is the most common endocrine disturbance, next to precocious puberty and accelerated skeletal growth and maturation. In the patients reported in the literature hyperthyroidism supervened some years after the initial recognition of polyostotic fibrous dysplasia. Pathologic examination of the thyroid gland has usually revealed either adenomatous hyperplasia or colloid goiter.

Although the etiology and pathogenesis of polyostotic fibrous dysplasia are unknown, most of the authors agree with the view held by Jaffe and Lichtenstein that this disease is the result of a developmental defect that manifests itself predominantly by the skeletal lesions, which are amplified by the various extraskkeletal abnormalities. In the case reported, thyrotoxicosis was a contributing factor to the patient's inability to walk, although it was not recognized immediately because of the extensive bone lesions. Numerous fractures of the long bones of the lower extremities occurred, but all showed bony union in a reasonable time. A normal amount of callus formed at each fracture site; however, it thinned out rapidly, suggesting either replacement by dysplastic fibrous tissue or rapid remodelling.

The osteoporosis seen in the present case was more marked than is ordinarily observed in fibrous dysplasia. This was undoubtedly the result of the primary bone disease and disuse atrophy, although it may have been accentuated by thyrotoxicosis. Skin pigmentation was present, but there was no sexual precocity. The initially elevated alkaline phosphatase dropped to normal when the fractures healed. Normal values of calcium and phosphorus were found in the serum and urine. The hypoplastic left testicle was noted as an associated anomaly, and paralysis of the right vocal cord was most likely the result of pressure caused by the enlarged thyroid.—*J. N. Ant, M.D.*

RIEDERER, J. Ein Fall von Pylescher kongenitaler familiärer Knochendysplasie (Pyle's disease). (A case of Pyle's congenital familial bone dysplasia [Pyle's disease].) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Sept., 1961, 95, 396-402. (Address: Dr. med. J. Riederer, Univ.-Röntgeninstitut am Bürgerspital, Basel, Switzerland.)

A case of Pyle's disease is described. There is com-

plete tabulation of the 36 cases reported in the literature.

The author considers his case as a "forme fruste." The only findings were abnormal tubulation of the extremities with abnormal growth in length, typical deformity of pelvis and abnormally fine trabeculation of the medullary structures. The name Pyle's disease seems incorrect because the cause is likely a developmental anomaly. A more adequate term would be Pyle's congenital familial osteodysplasia.—*Hans W. Hefke, M.D.*

FUCILLA, IVAN S., and HAMANN, ANNA. Hodgkin's disease in bone. *Radiology*, July, 1961, 77, 53-59. (Address: I. S. Fucilla, Evanston Hospital Association, 2650 Ridge Ave., Evanston, Ill.)

Hodgkin's disease involving every organ system including the skeleton has been reported. This discussion is based on a review of the literature and a study of 94 previously unreported cases of which 11 showed osseous involvement.

Pathologically both the gross and microscopic appearance of the lesions is the same as in nonosseous tissue, with the Reed-Sternberg cell being the diagnostic feature. In the spongiosa the disease may be widespread without giving rise to symptoms or roentgenographic signs. Cortical involvement is more readily detectable, with roentgenographic evidence found ante mortem in approximately 15 per cent of all cases of Hodgkin's disease. Bone involvement occurs throughout the course of the disease and its appearance does not significantly affect the prognosis. Pain with or without a mass and/or roentgenographic changes is the most frequent symptom. Occasionally large cortical lesions are found which have produced no signs or symptoms. The systemic symptoms and hematologic findings are substantially the same as in patients without detectable bone lesions. In the absence of liver disease an elevated serum alkaline phosphatase level strongly suggests bone involvement even when the roentgenographic examination is negative.

Hodgkin's disease spreads by contiguity and hematogenously. Invasion of bone occurs most frequently adjacent to the lymph node bearing areas, i.e., the spine, pelvis, sternum, ribs, and the inner halves of the clavicles. Scattered lesions not related to lymph node areas are considered to be of hematogenous origin, occur almost exclusively in the red bone marrow, and are usually small and asymptomatic. Primary Hodgkin's disease of bone has not been conclusively demonstrated.

Hodgkin's disease of bone presents no pathognomonic roentgenographic appearance. Since bone involvement is found occasionally before the diagnosis has been established, Hodgkin's disease should be considered in the presence of any bone lesion of obscure origin. The lesions are predominantly osteo-

lytic with areas of sclerosis in the margins, occasionally purely osteolytic, and rarely entirely osteoblastic in the vertebral bodies. Destructive changes are often accompanied by expansion, particularly in the ribs or sternum. Minimal periosteal new bone formation may occur and some spicule formation may be found suggesting osteogenic sarcoma. Multiple lesions are the rule, and mixed features may be present. The maximum incidence of bone involvement is in the upper lumbar and lower cervical spine, with mostly mixed lesions occurring in the vertebral bodies, sparing the disks. Involvement of the flat bones is primarily of an osteolytic type. Occasionally, a mixed type of lesion with periosteal new bone formation will mimic Paget's disease of bone. Differentiation between Hodgkin's disease and other lesions of bone, *i.e.*, metastatic cancer, multiple myeloma, reticulum cell sarcoma and other lymphosarcomas, and osteomyelitis (particularly tuberculosis) is most difficult.

The granulomatous tissue of Hodgkin's disease in bone is almost as radiosensitive as in other locations and responds well to moderate doses of radiation. Alkylating agents are of use in widespread disease.—*Walter H. Jarvis, Jr., M.D.*

COVENTRY, MARK B. Some skeletal changes in the Ehlers-Danlos syndrome; a report of two cases. *J. Bone & Joint Surg.*, Sept., 1961, 43-A, 855-860. (From: Section of Orthopedic Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minn.)

The author reports 2 cases of Ehlers-Danlos syndrome with thoracolumbar kyphoscoliosis as the result of anterior wedging of the vertebrae. In addition, he presents other skeletal abnormalities not previously described, namely, a long, giraffe-like neck, a downward sloping of the ribs of the upper part of the thorax, and a tendency to reversal of the normal cervical, thoracic, and lumbar spinal curves.

McKusick grouped certain inherited conditions involving the mesenchyme which he called "heritable disorders of connective tissue." These include the Ehlers-Danlos syndrome, the Marfan syndrome, the Hurler syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum.

In the Ehlers-Danlos syndrome the skin is velvety thin, hyperelastic, brittle, bruises easily and leaves scarring after subcutaneous hemorrhage. Molluscoid fibrous tumors develop over pressure points. The joints are hypermobile. Representative of this syndrome are the contortionists and Indian rubber men of the circus side show. Elbows and knees hyperextend and the thumb can be brought back to touch the forearm. Flat feet and habitual dislocation of joints are often observed. Additionally, changes occur in the ocular adnexa, the cornea, the sclera, the suspensory mechanism of the lens and the fundus. Most patients are tall but some are short. The basic

mesenchymal defect in the Ehlers-Danlos syndrome is probably a superabundance of elastic fibers in the skin and joint capsules, with an abnormal organization or network pattern of the collagen bundles. Perhaps, there is an abnormality in the collagen structure itself.

The changes relating to the connective tissue defect may occur in disorders other than this syndrome. Epiphysitis of the spinal column has been reported in the Marfan syndrome. Patients with osteogenesis imperfecta present a round back. In Hurler's syndrome there is thoracolumbar kyphoscoliosis, but this is characterized by a rather acute angle and is due to posterior displacement of one vertebra, which becomes acutely wedged anteriorly and produces a gibbus. The Marquio-Brailsford type of chondro-osteodystrophy is characterized by a similar change.—*J. N. Anté, M.D.*

KELLY, PATRICK J., JANES, JOSEPH M., and PETERSON, LOWELL F. A. The effect of beryllium on bone; a morphological study of the progressive changes observed in rabbit bone. *J. Bone & Joint Surg.*, Sept., 1961, 43-A, 829-844. (From: Section of Orthopedic Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minn.)

The authors report a series of roentgenographic and microradiographic studies of the long bones of 14 rabbits after injection of zinc beryllium silicate. Five milliliters of 1 per cent suspension of zinc beryllium silicate were injected into an ear vein of each rabbit twice a week for ten weeks. At the end of this time, each animal had received a total of 1 gm. of zinc beryllium silicate, or 33.6 mg. of beryllium expressed as the oxide.

Medullary formation of bone was detected on roentgenograms between eight and sixteen weeks after the last injection of zinc beryllium silicate in all 14 animals. These changes were seen in the diaphysis and in the proximal metaphyseal regions of the tibiae, humeri, and femora, and in one instance, in the ischium. Between the thirtieth and the fifty-second week after the last injection in 10 of the 14 animals, a destructive osteogenic sarcoma appeared suddenly. The endosteal bond had a higher mineral content than the surrounding cortical bone and did not exhibit as distinct a lamellar structure. Cleared specimens demonstrated a gradual isolation or encroachment of the nutrient vessels and their transverse or lateral branches by the abnormal medullary bone.

Three histologic varieties of osteogenic sarcoma were noted: osteoblastic, chondroblastic and fibroblastic. It was usual to find all three varieties in the same tumor. The relatively late appearance of osteogenic sarcoma may represent a continued cumulative effect from slowly released beryllium ions on the enzyme systems of the cells.—*J. N. Anté, M.D.*



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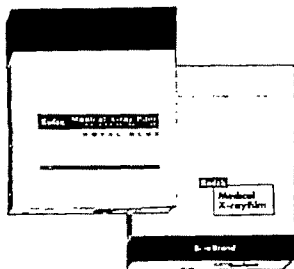
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Index:

DEXTER S. GOLDMAN: Enzyme Systems in the Mycobacteria.—A Review
J. N. VIVIEN et J. GROSSET, Paris: Le taux d'isoniazide actif dans le sérum sanguin
K. AUERSBACH, K. BARTMANN, G.-W. KAUFFMANN, A. KREBS, I. SCHÜTZ und
P. STEINBRÜCK, Berlin-Wannsee: Die frühere Erkennung des ungenügenden Effekts der
konservativ-chemischen Behandlung bei kavernöser Lungentuberkulose
M. F. MAGARAO, J. DAUSTER, A. C. SANTIAGO, E. WERNECK, H. FRAGA, A. P. ALMEIDA
and R. C. R. BARRETO, Rio de Janeiro: The Problem of the Resistance of *M. tuberculosis*
to Standard Drugs in Rio de Janeiro, Brazil
H. L. ISRAEL and M. SONES, Philadelphia, Pa.: Sarcoidosis
A. GEBAUER, Frankfurt am Main: Täuschungsmöglichkeiten im Röntgenschnittbild, ihre
Ursachen und ihre Vermeidung

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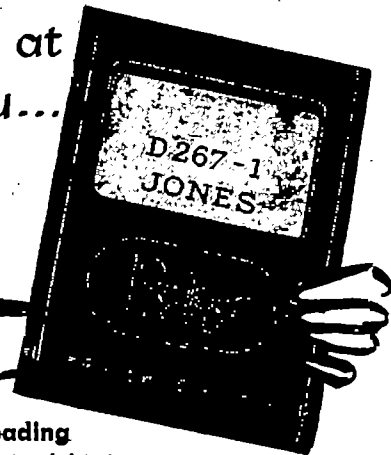
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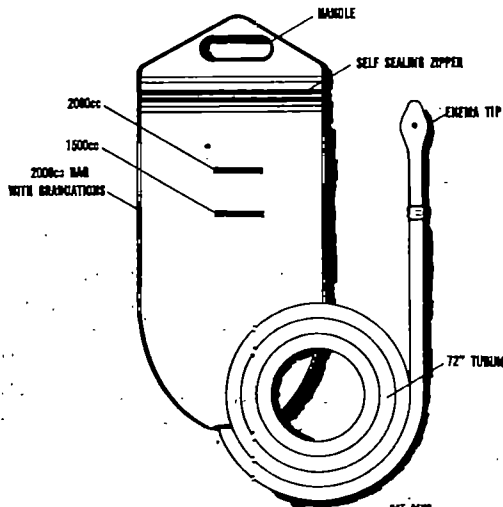
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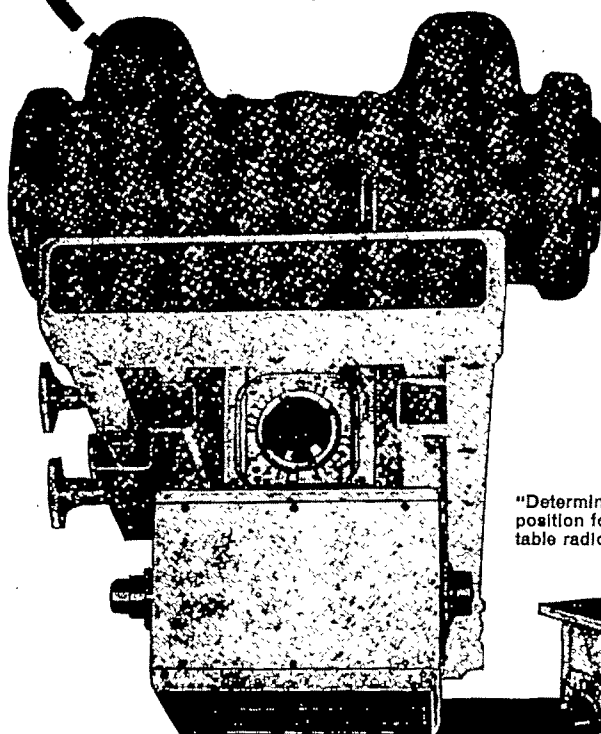
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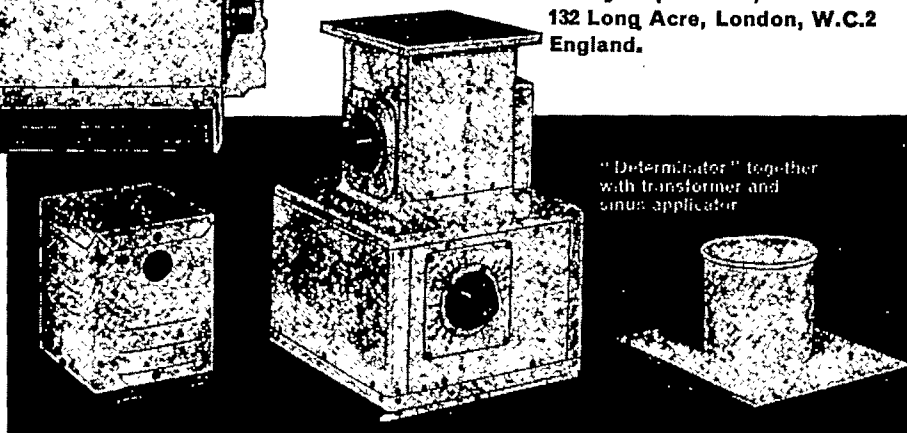
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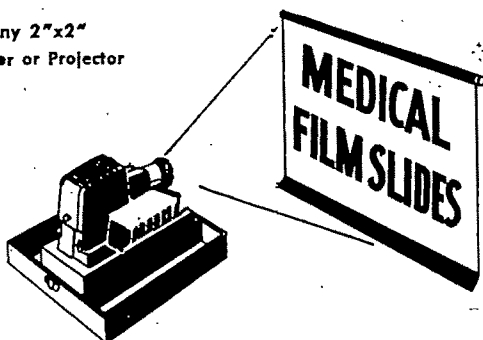
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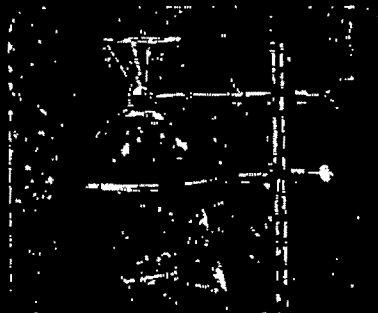
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INDEX TO ADVERTISERS

AnSCO (A Division of the General Aniline & Film Corporation)	xii, xiii
Atomic Accessories, Inc.	xl
Atomic Energy of Canada Ltd.	xxx
Atomium Corporation	xxxiv
Automatic Seriograph Corp. (Litten Industries)	Third cover
Associated Electrical Industries Ltd.	xl
Barnes-Hind Laboratories	1
Buck X-Ograph Company	xl
Du Pont de Nemours, E. I. & Co. (Inc.)	vi, xxxi, xxxii
Eastman Kodak Company	xxvii, xli, xlii
Fougera, E. & Company, Inc.	xiv, xv, xl
General Electric Company	viii, ix, x, xi, xxxvi, xxxvii
Hunt, Philip A., Company	vii
Ilford, Inc.	xxix
Karger, S.	xliii
Lafayette Pharmacal	xxvi
Liberty Protective Leathers, Inc.	xl
Liebel-Flarsheim Co. (Division of The Ritter Co.)	xxiv
Low X-Ray Corporation	xxviii
Machlett Laboratories	xxxv
Micro X-Ray Recorder, Inc.	xliv
McElroy, Donald, Inc.	xlvi
Nuclear-Chicago Corporation	xix, xx, xxi, xxii, xxxix
Old Delft Optical Company (Odelca)	xxxiii
Ortho Pharmaceutical Corporation	xvii
Pickering X-Ray Corporation	xxv, xliv, Fourth cover
Profexray, Inc.	i
Siemens New York, Inc.	xvi
Squibb, E. R. & Sons	v
Standard X-Ray Company	xxxiii
Thomas, Charles C, Publisher	xxxviii, xli
Union Carbide Corporation	xlvi
Walker Industries	xliv
Westinghouse Electric Corporation	Second cover
Winthrop Laboratories	xviii

We try to present an accurate index. Occasionally this may not be possible because of a last minute change or an omission.

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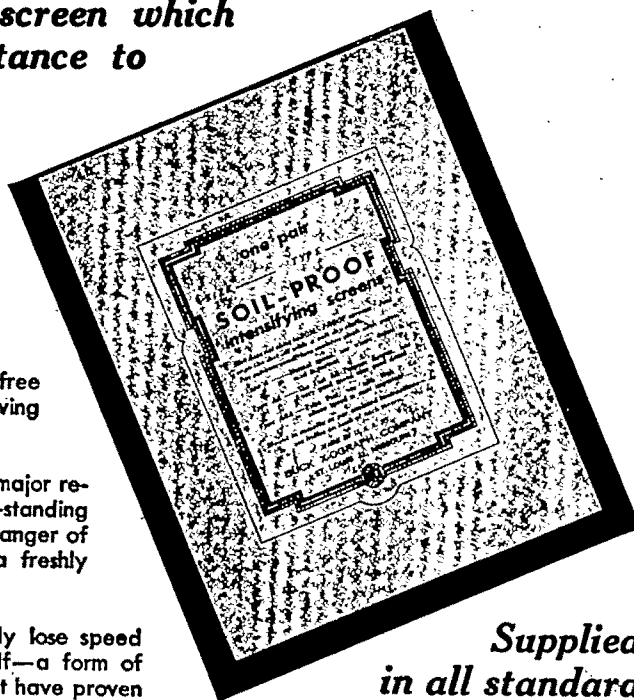
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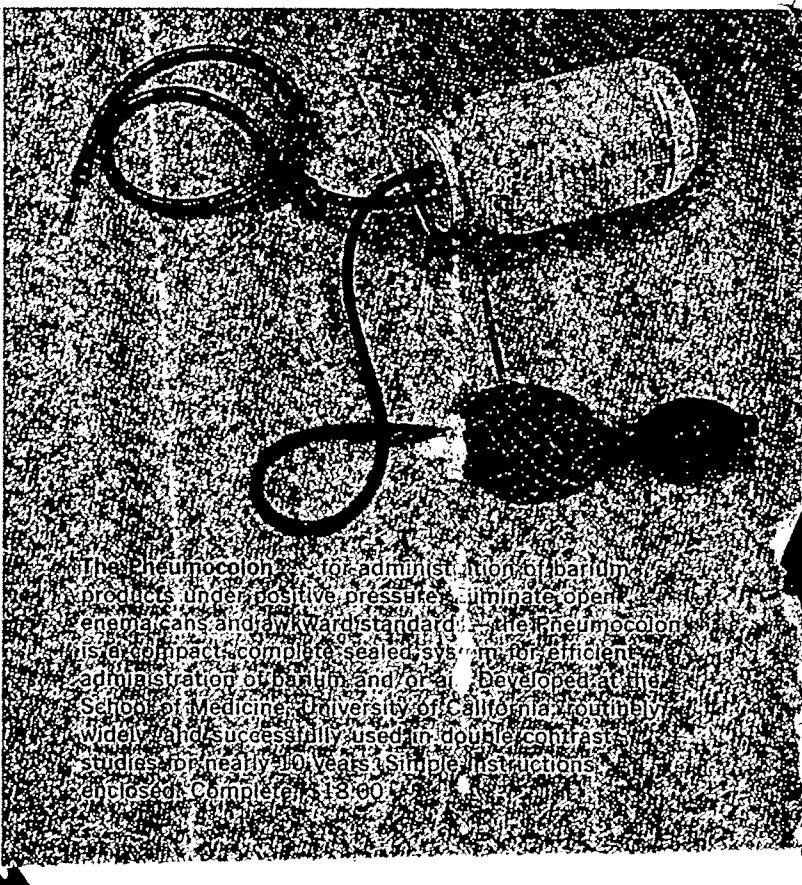
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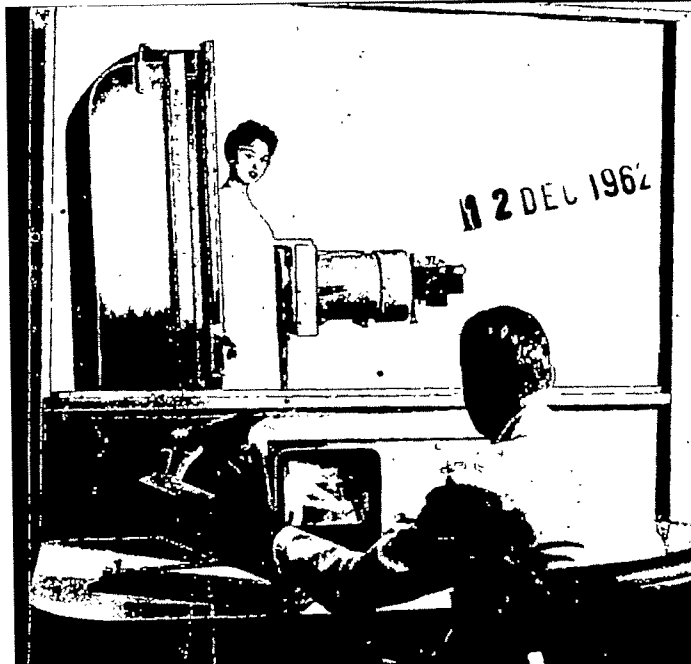
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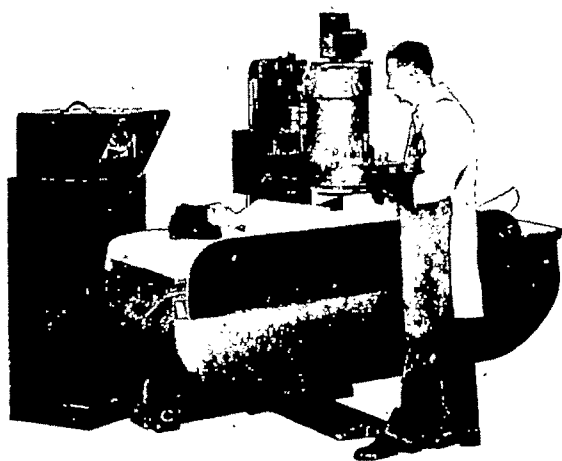
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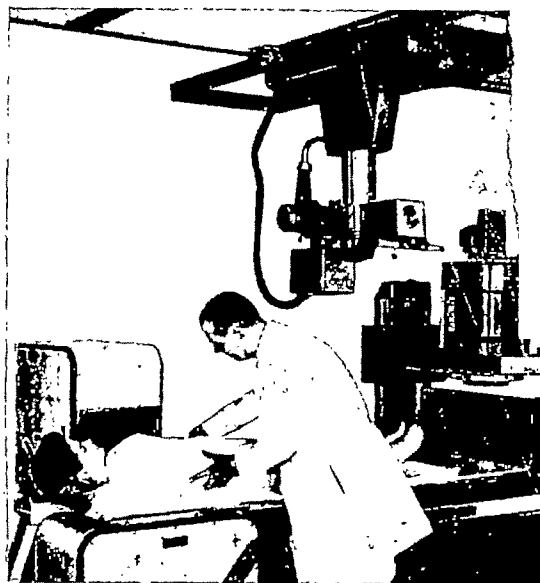
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